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COLIN RICHARD BLYTHE

OESOPHAGEAL CANCER:

WITH SPECIAL REFERENCE TO DEATHS IN SCOTLAND IN 1970-1974

Thesis submitted for the degree of

Master of Philosophy of The Open University

Department of Geography: Faculty of Social Sciences

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PREFACE

'...why oesophageal cancer in Scotland?'

Oesophageal cancer intrigues epidemiologists: probably no other cancer has a greater range of known and suspected risk factors, nor such elusive links with any of them. In the United Kingdom, studies of the disease in Wales in the 1960s produced tantalising associations with anaemia and Plummer-Vinson disease, metals in the soil and even 'degree of Welshness' (see Chapter One, section 1.5.3). When this study was proposed, oesophageal cancer rates in Scotland were twice those in England and Wales and rising: those in England and Wales were falling. The intrinsic interest of the subject, the growing Scottish death rate and the fact that almost nothing had been published on the subject in Scotland, all suggested that a geography of oesophageal cancer in Scotland might be rewarding. In the event it was frustrating.

Since little was known of the mortality pattern, the study had to begin with a basic description of the situation - and a hope that the pattern disclosed might have aspects worthy of further investigation. The author defends this approach, dismissed as 'dredging' by Jones and Rushton (1982), on grounds that to describe a hitherto unknown situation is always useful, provided it is done well. However, the fact that so many good epidemiologists had failed to establish an incontrovertible link between risk factors and spatial distribution of the disease should have warned against the investment of too much time!

Such geographical patterns as emerged might, of course, have more significance were they to re-emerge when mapped at different time

* Paula Cook-Mozaffari, personal communication, 1981.

periods. As the sequel narrates, an attempt at this had to be abandoned because of lack of funds to buy census material for a second period: however, the appearance of the Cancer Atlas of Scotland (Kemp et al, 1985) as the present study was approaching completion permits some consideration of this possibility. For the most part the Atlas shows very different spatial patterns to those found by the author.

Thus, on the evidence assembled by the author, there are no geographical correlates of oesophageal cancer in Scotland and the distribution of the disease is almost entirely random. The author hypothesises that the distribution of this cancer in Scotland reflects random occurrence within the population of a particular personality type, and that at the end of a long development period small clusters will generally crop up randomly in various unrelated parts of the country (though one possible exception is discussed later). Needless to say, this hypothesis is exceedingly difficult to verify.

Authors of research studies that after strenuous efforts produce such tenuous results must console themselves with the truism that negative results are nevertheless results, and that if well founded and well argued they are value to future researchers on the topic. A tinge of disappointment must and does remain, though the challenge and fascination of the subject have to some extent offset the many moments of frustration.

PART ONE

OESOPHAGEAL CANCER: LITERATURE SURVEY

CHAPTER ONE: CHARACTERISTICS OF OESOPHAGEAL CANCER: SPATIAL
DISTRIBUTION: TIME TRENDS: SOCIAL CLASS AND
OTHER MISCELLANEOUS CORRELATES

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CHAPTER ONE: CHARACTERISTICS OF OESOPHAGEAL CANCER: SPATIAL
DISTRIBUTION: TIME TRENDS: SOCIAL CLASS AND OTHER
MISCELLANEOUS CORRELATES

1.1.0 Characteristics of oesophageal cancer

Oesophageal cancer is a rapidly fatal disease: average survival time is less than six months from initial diagnosis and the overall survival rate after five years is less than 3% (Keller, 1980). Because of the rapid progress of the disease morbidity is virtually synonymous with mortality throughout the world. Doll (1969), using data from eight countries which had produced concurrent incidence and mortality rates, derived a factor of 1.9 to convert mortality at ages 35-64 years to incidence for the same age group. Warwick and Harington (1973) attribute the lethality of the disease to two factors: a) the tendency of the epithelium, whether of ecto- or endodermal origin, to give rise to freely metastasing tumours, and b) the generally late diagnosis of the condition. In its earlier stages cancer of the oesophagus is symptomless; progressive dysphagia and pain develop only in its advanced stages, by which time the original tumour is probably to invasive to treat and has, in any case, almost certainly metastasised extensively. Evidence from China, where an ambitious screening programme is in operation in Linxian County, suggests that diagnosis at the very earliest stages of the disease somewhat improves chances of survival (Waterhouse, 1974 - quoted in Cook-Mozaffari, 1980).

1.1.1 Some implications of tumour siting

Clinical observation shows that most oesophageal tumours arise at or just above points where the oesophagus narrows (Oettlé, 1967). The narrowing may be natural (e.g. at the level of the left bronchus), or may be due to injury (e.g. following ingestion of lye, or after chronic gastric reflux). A higher risk still is associated with conditions which lead to food stagnating in the oesophagus, for example food stasis resulting from the presence of diverticula, or from achalasia of the gastric cardia (failure of the cardiac oesophageal sphincter to relax). As Oettlé points out, these facts are consistent with the surface/topical action of an ingested carcinogen, rather than any systemically acting carcinogen affecting the oesophagus alone. Day (1984) believes that '...micro-nutrient deficiencies or imbalance provide a unifying explanation of the epidemiology of oesophageal cancer.' Day is almost certainly right to stress the primacy of nutritional status in the development of the disease - wherever it is found - but this is not to say that intrusive carcinogens or agents of trauma are not also important, even essential. Malnutrition alone, however important for establishing the conditions which predispose to tumour development, is insufficient to explain the siting of tumours at constrictions within the oesophagus.

Oettlé (op cit) classifies oesophageal tumours under three main headings:

- 1) squamous-cell carcinomas of the cervical oesophagus, associated with iron deficiency (sideropaenia).

- 2) squamous-cell carcinoma of the thoracic oesophagus, attributable (in Oettlé's view) to ingested carcinogens.
- 3) adenocarcinoma, usually of the diaphragmatic oesophagus (and possibly invasive from the stomach).

There is a fourth, small class of miscellaneous rare tumours such as sarcoma and melanoma.

As will be seen later, there are grounds for considering the first category - carcinoma of the cervical oesophagus with associated sideropaenia - as a distinct aetiological entity. Further implications of tumour site are considered in the chapters on diet, alcohol and tobacco.

1.1.2 Genetic factors

There is virtual unanimity that oesophageal cancer is due mainly to external factors, however, some authors have considered the possibility that the response of individuals may be genetically determined. Ashley (1969) suggested that high mortality from the disease in parts of Wales could be related to a genetic factor involving one or more genes carried on the X chromosome. Petrakis (1971), however, found no relationship between genetic make-up and incidence of cancers of the cervix, lung, stomach, large intestine, rectum, oesophagus and prostate among American blacks.

In one rare syndrome only has a genetic factor been indicted: individuals with tylosis (abnormal keratinisation of the palms and

soles) may later develop oesophageal cancer. The condition is familial and the mode of inheritance shown to be through an autosomal dominant gene (Mulvihill, 1975), so that in families in which it occurs it is not uncommon for more than one member to be affected. A substantial proportion of people with tylosis develop oesophageal cancer: 30% in one study (Clarke et al, 1957). In general, however, the condition is sufficiently rare to warrant no further mention here.

Other than the instance just cited, no simple pattern of inheritance has been found: however, because cancers are common in certain regions, it is to be expected that close relatives will be affected by a particular disease even if heredity were not directly implicated (McConnell, 1966). McConnell (op cit) found 1,882 cases in a population of 1.6 million over a five-year period (24/100 000 per annum) in the Transkei. The cases were distributed in scattered foci of high incidence, suggesting that genetic factors might be present in greater concentrations than elsewhere. However, in 71 instances, McConnell found households with two or more affected but unrelated members, suggesting that some local external factor was responsible, rather than any shared genetic predisposition.

1.1.3 Oesophageal cancer in animals

Cancer of the oesophagus has been experimentally induced in laboratory and domestic food animals and the results have yielded important information about the effects of nutritional deficiencies and suspected carcinogens (reference is made to some of the results in

Chapters Two and Three): the disease has also been detected in wild animals and domestic animals in non-experimental situations. An epidemic of oesophageal cancer among Masai cattle was reported by Plowright et al (1971) but no plant or parasite was found which could be implicated. The disease had apparently been known to the Masai since 1935 and was confined to one valley: humans and buffaloes were not affected but two cases were reported among giant forest hogs! (Warwick and Harington, 1973). Efforts to discover the cause of oesophageal cancer among chickens in Linxian County (Honan Province) produced strong evidence that a mycotoxin was implicated and might also be a principal aetiological agent among humans in Northern China (Miller, 1981). Other workers believe that an alternative explanation - silica fragments from millet - satisfactorily accounts for oesophageal cancer in chickens and humans in Linxian (O'Neill et al, 1982): these arguments are reviewed in more detail in Chapter Two.

1.2.0 Some general aspects of worldwide distribution

Although uncommon in white caucasian populations, Day (1984) points out that a recent WHO estimate places oesophageal cancer seventh in order of frequency of occurrence worldwide (both sexes combined), so that the disease may justifiably be termed a 'common cancer'. The distribution of oesophageal cancer is remarkable, it has the most extreme range of incidence of any common cancer, the steepest gradients of incidence between affected and unaffected areas, and in all but some of the highest incidence areas male and female rates are very dissimilar (figures for incidence/mortality rates and for

male/female ratios are given below).

The steep gradients which characterise the spatial distribution of oesophageal cancer should, in theory, make the discovery of causal agents easier. Day (op cit) writes that this cancer is '...the malignancy par excellence where geographical pathology should illuminate the aetiology.' Alas for theory: as well as the unique attributes of its distribution, oesophageal cancer must also be first among tumours with multi-causal origins. Although nutritional deficiency or imbalance is now accepted as a necessary precondition of almost all oesophageal cancer (Day, op cit), the suspected carcinogens and agents of insult and trauma - and indeed the causes of the nutritional deficiencies and imbalances themselves - are more varied than for any other cancer.

In many countries oesophageal cancer is obviously linked to consumption of alcohol and tobacco, with striking dose-response relationships seen for both substances, alone and in combination (see Chapters Three and Four). Indeed, from data reviewed in succeeding chapters it is apparent that cancer of the oesophagus hardly occurs among well-nourished, non-drinking, non-smoking white males in Europe, North America and Australasia. Some of the highest incidence areas, however, have Islamic populations, to whom alcohol is proscribed and among whom tobacco has been found to exert a negligible effect on the development of the disease (Cook-Mozaffari, op cit; Mahboubi and Aramesh, 1980). From this it is evident that alcohol and tobacco are not essential to the development of the cancer, nor, worldwide, are

they necessarily the most important determinants of the disease.

Even in countries where the alcohol-tobacco link is very strong, there are some curious anomalies. Alcohol and tobacco show the same clear dose-response effect on cancers of the mouth, pharynx, larynx and lung, yet there is little uniformity in the spatial relationship of these cancers with oesophageal cancer. In France and Switzerland, for example, high rates of oesophageal cancer are associated with high oral cancer rates - an association not seen in Japan or Chile, where relatively high oesophageal cancer rates co-exist with low oral cancer mortality (Oettlé, 1967). In Poland, where alcoholism rates are exceptionally high, and where there are also high and rising rates of lung and laryngeal cancer, oesophageal cancer rates have been declining steadily over a long period and are now low (Day, op cit, quoting Zatonsky).

1.2.1 Urban and rural rates

Over much of the world no clear urban-rural gradient emerges. In the Central Asian oesophageal cancer belt rates may be equally high in either urban or rural areas: the highest rates in the world are found in the refinery and petrochemical town of Gurjev in Kazakhstan, but rates very nearly as high also occur in the arid steppelands of Gonbad in north-eastern Iran. High rates in China seem to be mainly a rural phenomenon, but in South Africa the high rates in rural Transkei and Ciskei are matched by those in Durban and Johannesburg (Bradshaw et al, 1983). In the moderately high-incidence areas of

the Caribbean (Puerto Rico and Curacao) the disease occurs principally among the rural poor.

In the United States, however, there is a pronounced urban-rural gradient (Lynch et al, 1971; Schoenberg et al, 1971). Schoenberg et al (1971) found that alcohol, tobacco and urbanisation were positively correlated with oesophageal cancer: more surprisingly, when the authors controlled for alcohol and tobacco, only urbanisation remained significantly correlated with the disease ($p < .001$). Schoenberg et al concluded from this that risk factors other than alcohol and tobacco (e.g. air pollution and certain occupations), played an important, perhaps decisive role in the development of this cancer. An urban-rural gradient is also found in much of Europe: Day (1975) found oesophageal cancer positively correlated with poor living standards and that those most affected were the lowest classes of urban populations. This otherwise uniform picture was spoilt, however, by relatively high rates (the highest in Europe) in rural Brittany and Normandy, and in the rural areas around Bolzano, Trento, Trieste and Verona in north-eastern Italy. In England and Wales the picture is very unclear: parts of rural Wales, Cornwall, Kent and Cumbria have anomalously high rates, but so also do the Merseyside conurbation and parts of East London (see maps in Gardner et al, 1983).

In Scotland there is a marked urban-rural gradient, although, since the bulk of the population lives in the cities and towns (whose

aggregate rates therefore approach the norm), the urban areas are less conspicuous for having high rates than are the rural areas with their strikingly low rates. The Scottish urban/rural gradient is described in sections 7.3.0 (Table 32) and 7.4.0 of Chapter Seven.

1.2.2 Class and race

Over most of the world oesophageal cancer is a disease of the poor, even in affluent societies those mainly affected are from the lower socio-economic groups. Oettle (op cit) writes: '...social class is merely a pointer to environmental exposure.' Though perhaps something of an over-simplification, the remark is essentially true. It is lower income workers who are more likely to have jobs which involve exposure to carcinogens and who, with their families, are likely to have inadequate or unsuitable diets (even in the United Kingdom - Cannon and Walker (1985)). As genetic factors may effectively be ruled out, together with any significant correlation with blood group (see section 2.4.1), differences in inter-racial mortality within countries can be assumed to result from socio-economic and cultural factors. Disparities in income, housing, diet and consumption of alcohol and tobacco correlate well, for example, with observed differences in cancer mortality between blacks and whites in the USA (see, among others, Lynch et al, 1971; Schoenberg et al, 1971; et al, 1977; Feldman & Boxer, 1979; Tuyns, 1979; Keller, 1980 and Thind et al, 1981).

In England and Wales oesophageal cancer is predominantly a disease of social classes III-V (HMSO/IARC, 1982): likewise in Scotland, the disease is almost exclusive to manual workers and to people in the service industries. The contrast between the incidence in manual and non-manual occupations is striking: for example, administrative and professional workers (occupation units 173-220) constitute about 17% of the Scottish workforce but contribute less than 8% of the oesophageal cancer deaths (Author's findings: see section 6.3.5).

1.2.3 Incidence ratios and sex

In areas of the very highest incidence (e.g. the Central Asian oesophageal cancer belt, parts of northern China and southern Africa) male and female rates are roughly comparable, but over much of the rest of the world oesophageal cancer is a disease which mainly affects men. The highest sex incidence ratios are seen in parts of France (Calvados, Orne, Ille-et-Villaine), where male rates may exceed female rates by a factor of 20 or more. In the Italian province of Trieste male rates are more than 10 times the female rates. Very seldom is the sex ratio reversed, and then never in high-incidence areas. Israeli Jews born in Africa have a male/female incidence ratio of 0.09, but the incidence among all Jews is very low (Cook-Mozaffari, 1980). An apparently high female preponderance among Alaskan Eskimo women - often quoted (and attributed to chewing sealskin prepared with ashes) - was in fact based upon only 9 cases (7 female) (Hurst, 1964). In parts of North Wales female rates may be somewhat higher than the male, but - as explained in Chapter Five - it is difficult to get a true picture (in any case, rates are liable to be very unstable because of the small numbers involved).

1.3.0 Areas of very high incidence: Southern-Central Asia (Iran, Kazakhstan, Turkmenistan)

Not only are oesophageal cancer levels around the Caspian Sea the highest in the world, but the levels of incidence are the highest for any type of cancer observed in general populations (i.e. as distinct from groups with specific genetic, environmental or occupational risks). The gradients are also extreme, both in range and steepness. Between Gurjev town in Kazakhstan and the towns of Georgia 500 miles away, the incidence drops 70-fold for men and 230-fold for women. Between Honan and Shansi in northern China, a distance of about 300 miles, there is a 60-fold drop for men and a 90-fold drop for women (Cook-Mozaffari, 1980).

In complete contrast to the situation in South Africa (see below), rates in Iran appear to be very stable; the disease is apparently described in Persian medical textbooks of the 12th century (Cook-Mozaffari, 1980 - citing Elgood, 1951).

Although at the lower levels the disease seems to cut across ethnic boundaries, Day (1984) writes that at the highest levels it is seen almost exclusively in groups of Turkic origin - Turkoman, Uzbek and Kazakh - and not among groups of Indo-European origin - Persian, Pathan and Russian. If genetic predisposition is not involved, then the cause(s) must lie in something common to the lifestyles of the Turkic groups but absent from the lives of the other groups.

In northern Iran, cancer of the oesophagus is negatively correlated with rainfall, and in consequence there are also associations with rainfall-dependent variables such as vegetation and crop types, and whether agriculture is settled or semi-nomadic pastoralist (Cook-Mozaffari, 1979). Aridity seems to be a factor linking the high-incidence areas of China and South Africa. The Xhosa of Transkei have suffered from drought and soil erosion over many years (Bradshaw et al, 1983) and in China aridity increases the further north one goes (although conditions in the high-incidence areas of China do not appear to be as dry as those in Iran).

Common to all three high-incidence regions are cereal-based diets: in the Soviet, Iranian and Chinese areas the staple is wheat, in South Africa maize has increasingly replaced sorghum. In China and southern-central Asia coarse dark bread forms the bulk of the diet, along with tea and sugar (Cook-Mozaffari, 1979). Apart from the fact that such a diet is inadequate to maintain health, it is possible that the bread may also contribute an element of mechanical trauma. O'Neill et al (1982) believe silica fragments in cereals could provide a unifying link between several of the high-incidence areas.

Mahboubi and Aramesh (1980) provide a long list of factors which have been investigated in Iran; among these are: climate, geology and soil, vegetation and crop types, nutritional deficiencies, environmental carcinogens (nitrosamines, polycyclic hydrocarbons, aflatoxins), genetics, tobacco, tobacco and lime mixture, opium and

opium dross, alcohol, felt and carpet making, very hot tea, diet in pregnancy, geophagy and eating raw rice. No single factor was identified which could - on its own - adequately explain the pattern and range of incidence. Mahboubi and Aramesh propose that a complex of factors may be responsible and, moreover, that the complex may not be entirely the same for men and women. Poverty and poor diet (in particular a lack of fresh fruit and vegetables) appeared to be the only constant features.

1.3.1 Southern Africa

In parts of Africa (e.g. most¹ of the west coast, including Nigeria) oesophageal cancer is almost unknown, while in other areas its incidence is very low (Mozambique, Tanzania, Uganda). In a few areas, however, incidence rates range from moderate to some of the highest in the world (the Transkei, Cape Province, Central and Western Kenya, Southern Malawi and the cities of Bulawayo, Durban and Johannesburg. Apart from the peculiarities of its geographical distribution, there are two other notable features of oesophageal cancer incidence in Southern Africa: its exceptional increase over time and the seeming arbitrariness of the sex ratio from one area to another.

Many authors relate that the disease 'appeared from nowhere' in the 1950s. Isaacson (1982) says that prior to 1950 cancer of the

1. A recent paper (Cornet et al, 1983) appears to suggest that a hitherto unremarked pocket of moderate incidence may exist in the Ivory Coast: home-made palm wine and maize liquor, as well as mouldy food are suggested as contributory agents.

oesophagus was a rarity in black populations and that, for example, between 1912 and 1927 not one case was diagnosed in black patients attending the South African Institute for Medical Research in Johannesburg. Since 1950 the disease has assumed epidemic proportions, with annual rates in the Transkei exceeding 245/100 000 in men aged 35-64 (Cook, 1971 - quoted in Bradshaw et al, 1983). The sudden emergence of the disease led to intensive searches for intrusive carcinogens and many clues were pursued, among them aflatoxins, nitrosamines, toxic metals in home brewed and distilled alcoholic beverages, herbal emetics and some practices associated with smoking: some of the possible risk factors are considered in more detail in later chapters.

In some areas cancer of the oesophagus is confined almost exclusively to males. Day (1984) gives a male incidence rate of 63.8/100,000 in Bulawayo, and a female rate of only 2.2/100,000. Elsewhere in South Africa female rates rise in parallel with male rates, though from lower levels. In the Butterworth district of Transkei the male incidence rate exceeds 180/100,000, with a male/female ratio of 2.3 (Cook-Mozaffari, 1980).

The Xhosa of Transkei and the Zulus of Natal are the peoples most affected in South Africa: they share some features of life in common with the Turkomans of Gonbad. All three groups live in areas subject to drought, and all have poor diets, short of protein, fats and many vitamins. Among the Xhosa maize is the staple and the susceptibility

of people on maize diets to pellagra has been long known, as has the association of pellagra with damage to the oesophageal mucosa (Warwick and Harington, 1973). Xhosa children are, even now, considerably affected by kwashiorkor and marasmus (Bradshaw et al, 1983). It is difficult to discover whether malnutrition has always been a factor in the lives of the Xhosa and Zulu, or whether food shortages are of comparatively recent origin, the result of protracted drought or the adverse effects of social and economic policies applied to blacks. One significant difference between South African blacks and the Turkomans is that the former are known to drink alcohol, sometimes heavily: Turkomans, in theory, do not.

Body iron levels are obviously critical in the development of oesophageal cancer, the disease being associated both with iron deficiency and iron overload (anaemia and sideropaenia are discussed in Chapter Two, section 2.3.3-2.3.5). There are a number of routes to excess iron levels (siderosis) but 'Bantu siderosis' is a form of iron overload of the hepatic cells - often resulting in liver fibrosis - in which the excess iron is thought to derive from cooking pots, with protein malnutrition and heavy alcohol intake as predisposing factors (Butterworths, 2nd ed., 1978). The complex inter-relationship between alcohol, liver function, iron levels, micro-nutrient status and epithelial integrity is a theme which appears repeatedly in this literature review.

There is no obvious urban-rural gradient in South Africa and migration from the high-incidence rural areas is not sufficient to account for the prevalence of the disease in the cities: black patients in one Johannesburg survey had lived, on average, nearly twenty years in the city (Oettle, 1963). However, the mortality experience of shorter-stay migrants in the Transvaal does, to some extent, reflect the situation in their place of origin: expatriates from low-incidence areas in north-eastern Transkei show significantly fewer cases than those from the south-west (McGlashan and Harington, 1975).

Kmet (1970) felt that the sharp borderlines between high- and low-incidence areas held out the best promise of isolating the aetiological agent(s). Despite the many clues investigated, however, only malnutrition appears incontrovertibly connected with the disease. Bradshaw and Harington (1983) are convinced that the high incidence and vagaries of distribution can be explained by reference to smoking habits, and on the basis of answers received from their study group, the arguments are persuasive: however, blacks presumably were smoking before the 1950s. If the predisposing condition - say, malnutrition - has been there all along, then the sudden emergence of the disease must have been triggered by the arrival of an intrusive carcinogen: if the carcinogen - say, tobacco tar - had been there all the time, then the rise of the disease must date from the emergence of a predisposing condition such as malnutrition. More, possibly, than in any other location, an 'event' in time holds the clue to oesophageal cancer in South Africa.

Finally, it now appears that the differentials are narrowing and, as rates in some formerly low-incidence areas begin to rise, the spatial patterns which held such promise for epidemiologists are beginning to blur and disappear (Day, 1984).

1.3.1 China

Oesophageal cancer is the second most common cancer in China, after stomach cancer (Day, 1984). In fact the overall incidence of the two cancers is very similar (around 32/100,000 in males, and 16/100,000 in females), but whereas stomach cancer is found in almost every part of China - and the incidence gradients are very smooth - oesophageal cancer is absent over large areas and occurs in localised pockets of exceptionally high incidence. The Chinese high-incidence areas share some features in common with the high-incidence areas of Iran and South Africa mentioned above: dry climatic conditions and a poor, monotonous diet. Yang (1980) and Fong (1982) describe the diet in general terms: cereal staples (maize, wheat and millet), with very small amounts of fresh vegetables (mainly eggplant, string beans, chinese cabbage and some potatoes) and 'pickled' vegetables (see Chapter Two, section 2.1.7): the diet is also low in animal products. However, as elsewhere, the simple equation of poor diet with high oesophageal cancer incidence will not hold in China: detailed dietary research and analysis of blood samples (Yang et al, 1982) has shown very few differences in food habits and nutritional status

between groups in the high-incidence area of Linxian² (overall rate 138/100,000, male/female ratio 1.6:1) and those in the comparatively low-incidence area of Fanxian some 150 km to the east (overall rate 24/100,000, male/female ratio 3.6:1). Yang et al (op cit) suggest that, although there were some vitamin deficiencies among the Linxian cancer group, the average nutritional status of families with oesophageal cancer victims was no worse than that of non-cancer families in Linxian, nor that of the low-cancer population of Fanxian. The similarity of diet and nutritional status between groups of such dissimilar cancer experience argues powerfully for acceptance of intrusive carcinogens and/or agents of mechanical trauma as part of the aetiological hypothesis, a conclusion already reached by Oettlé (1967) from the quite different starting point of tumour siting (section 1.1.1). Possible carcinogens and traumatic agents in China are discussed in Chapter Two, sections 2.1.7 and 2.2.2 respectively. Kaplan and Tsuchitani (1978) and Yang (1980) found that alcohol, although not proscribed, was little drunk in Linxian, nor did they find any strong correlation of oesophageal cancer with tobacco smoking: in these respects the Chinese situation differs greatly from that in the oesophageal cancer pockets of South Africa.

1.4.0 Areas of moderate incidence - Puerto Rico & Curacao

Rates in Puerto Rico approach 30/100,000 in males, with a male/female incidence ratio of 2.7:1 (Cook- Mozaffari, 1980). Estimates of rates

2. The author has followed the spelling of Chinese authors (e.g. L.Y.Y. Fong and C.S. Yang) writing in English. Thus: Linxian and Fanxian, rather than the Linhsien and Fanhsien of the older system.

in Curacao differ by a large margin: Cook-Mozaffari (1980 - quoting an IARC report of 1970) gives a male rate of 44.4/100,000: Warwick and Harington (1973 - citing O'Gara, 1968) quote 18/100,000 for males, with no mention of the male/female ratio. The male/female ratio in Curacao resembles those in the high-incidence areas of France, Switzerland and Yugoslavia: areas where the disease is virtually confined to men. By implication, in such areas, the chain of causation is to be sought in those habits, consumption patterns and occupations not shared by the sexes. In Puerto Rico the disease appears strongly correlated with poverty and under-nourishment: Fernandez (1975) measured low intakes of vitamin A, riboflavin, iron, calcium and calories. Martinez (1969) indicted illicitly distilled rum and found a strong correlation with alcohol even after controlling for tobacco use. Morton (1973 - cited in Berg, 1975) suggested heavy consumption of hot medicinal teas might be a causal factor in Curacao: he also mentioned the pervasive air pollution from the petroleum industry.

1.4.1 Singapore

Cook-Mozaffari (1979) quotes incidence rates of 30.0/100,000 for Singapore Chinese males, but only 7.9 and 4.4/100,000 for Singapore Indians and Malays. Within the Chinese community there is considerable variation between groups according to their area of origin in China, with rates of 30.7/100,000 among male Teochew speakers (N.E. Guandong Province) and only 4.5/100,000 among male Cantonese speakers. There is also a marked variation according to place of

birth, with Singapore-born Chinese having only 40% of the oesophageal cancer risk of the China-born (Day, 1984). Smoking, drinking (in particular strong traditional spirits) and low economic status have been implicated in case-control studies (Fong, 1982 - citing Morton, 1958 and de Jong et al, 1974). For the Singapore-born to have lower rates than their China-born parents and peers suggests either that their habits have altered in such a way as to reduce intakes of whatever carcinogens may have been present in China, or that the lifelong nutritional status of the Singapore-born is much better than that of the China-born (which in turn carries the implication that the foundations for this disease are laid early in life).

1.4.2 Japan

Average rates for Japan are rather low (7.2 and 2.2 per 100 000 per annum for males and females respectively (Shigematsu, 1977)) but there are locally high rates (in excess of 20/100 000 per annum in males) in Miyagi and Wakayama prefectures and in the south-western Kii Peninsula (Wynder & Hirayama, 1977; Nagai et al, 1983). Smoking patterns do not explain the spatial distribution of oesophageal cancer in Japan (Wynder and Hirayama, op cit) and the search for aetiological agents has concentrated on alcohol and certain traditional foods. In general, Japanese consume less alcohol than Americans but have higher rates of liver cirrhosis: this may be due to some endemic hepatic virus or to nutritional deficiencies (Wynder and Hirayama, op cit). Traditional spirits proved strongly

correlated with oesophageal cancer in Japan (Kono and Ikeda, 1979), just as they had among Singapore Chinese (see above). Dietary studies in Japan have produced puzzling results. In many countries oesophageal cancer is associated with poor diets and, in particular, with protein shortage and a lack of fresh fruit and vegetables. However, while Nagai et al (op cit) found positive associations with items that had aroused suspicion elsewhere (e.g. salty food, soy sauce and pickled vegetables), more surprisingly they also discovered positive correlations with wheat, pork and beef. Green vegetables, considered prophylactic in other countries, were weakly but positively correlated with the disease among females and had, seemingly, no influence either way on the disease in males. Pickles and other factors such as hot tea, hot gruel and bracken are considered in more detail in the next chapter (sections 2.1.7, 2.2.3 and 2.2.4).

1.5.0 Selected areas of generally low incidence: The United States, Australia and Europe

The United States

Oesophageal cancer rates are low over most of the USA, with a slight upward gradient towards the north-east. Death rates among whites have been stable over many years, but among blacks rates have been rising steadily for the past three decades. Mention was made in section 1.2.0 of the apparent lack of spatial concordance in many countries between cancers of the mouth, pharynx, larynx, oesophagus and lung. This feature is also seen in the USA, where blacks and

whites share similar risks for cancers of the mouth and pharynx (with fairly uniform rates over the whole country), but black males are at an inordinately greater risk of oesophageal cancer - which also shows wide geographic variations (see reference to Cutler & Young below).

Incidence rates per 100 000 population for the USA as a whole are given in the Third National Cancer Survey (Cutler & Young, 1975a):

Table 1: Age-adjusted incidence rates per annum
by race and sex: USA 1979-1971

White males	4.7	White females	1.3
Black males	16.7	Black females	3.7

In each case the black rates are about three times higher than the white rates, and in both races the disease is about three times more common in males.

Cutler and Young (1975b) surveyed cancer incidence in seven metropolitan areas of the USA (Atlanta, Birmingham, Dallas/Fort Worth, Detroit, Minneapolis/St Paul, Pittsburgh and San Francisco/Oakland) and two entire states (Iowa and Colorado). Among whites, oesophageal cancer shows a fairly narrow geographic range, with highest rates per annum (5.0/100 000) in Pittsburgh and lowest rates (2.9/100 000) in Iowa. Among white females rates are very low, nowhere higher than 1.3/100 000 and down to 0.6/100 000 in Colorado. For blacks the picture is very different: lowest male rates occur in Dallas/Fort Worth (15.0/100 000), highest in Pittsburgh and Atlanta (20.8 and 20.1/100 000 respectively).

Cook-Mozaffari (1980 - citing Waterhouse et al, 1976) gives even higher rates for black males in the San Francisco Bay area (27.9/100 000). Rates for black females vary from 5.6/100 000 in Pittsburgh, to 2.7/100 000 in Dallas/Fort Worth.

The strong correlation between oesophageal cancer and urbanisation in Western countries has already been mentioned (Schoenberg et al, op cit). Hoover et al (1975), working with data at the (US) county level, sought to refine the evidence further by relating age-adjusted mortality rates to the proportion of people living in urban and rural areas. The expected urban-rural gradient emerged, with county mortality rates rising or falling with the overall proportion of the population living in towns. To the authors' evident surprise, however, there was a confounding effect with social class (as inferred from years of schooling completed), with the longest-educated whites having higher rates than the least educated: this finding applied across the urban-rural spectrum.

Wynder and Bross (1961) pointed out that oesophageal cancer rates throughout the West had not risen with tobacco consumption, nor followed the steep upward trend of lung cancer (the complex relationship of smoking to oesophageal cancer is discussed in Chapter Four). The relationship of the disease to alcohol consumption seems more consistent - though even here there are curiosities, like the situation in Poland previously mentioned. In the USA Keller - among many others - believes that excessive whisky

consumption is the probable explanation for the high rates among black males (Keller, 1980). Nutrient deficiencies, for the most part alcohol-promoted, have been identified in oesophageal cancer patients from all affected groups: Blot and Fraumeni (1981) report that one third of oesophageal cancer patients in a Washington survey drank more than a pint of whisky a day.

1.5.1 Australia

Australian rates for oesophageal cancer are comparable with those in England and Wales, indeed, the mortality experience of successive cohorts in both countries closely resemble each other (see Chapter Three). Time trends for all upper alimentary tract cancers in Australia reveal an absolutely clear and positive relationship with trends in alcohol consumption (McMichael and Hetzel, 1978): trends for cancers of the mouth, pharynx, larynx and oesophagus do not, however, correspond at all with trends for lung cancer (Hetzel, 1978 - quoting Field (unpublished).)

Between 1965 and 1975 indices for all alcohol-related diseases rose in Australia: alcoholic psychoses by 4.1%, alcoholic beri beri 16.7% and alcoholism 54.8%. Deaths from all types of liver cirrhosis (of which - in Australia - 50% are thought due to alcohol) rose by 72% in the same period (Australia, Department of Health, 1976). Cross-correlations between alcohol, beverage type, liver cirrhosis and oesophageal cancer in Australia are referred to in Chapter Three, sections 3.3.6 and 3.3.8.

1.5.2 European Countries other than those in the United Kingdom

Incidence rates, time trends and the spatial distribution of oesophageal cancer in France, Italy and Norway are discussed in Chapter Three (Alcohol), while the mortality of Swedish women from the disease is referred to in Chapter Two (Diet - sections 2.3.3 and 2.3.4 on iron-deficiency anaemia and Plummer-Vinson syndrome).

1.5.3 England and Wales

Male death rates in England and Wales declined steeply from about 1920 until 1950. From around 1960 male rates began to rise again, but are still some way below those found at the start of the century. There is evidence of a cohort effect for men, with mortality increasing for cohorts born after 1905: the lowest death rates are seen for men born in the last quarter of the 19th century and the first five years of this century. The overall trend in female rates is much less clear, with younger and older age groups diverging for much of the century. Chilvers et al (1979) found that cohort mortality in both sexes is strongly and positively correlated with per caput alcohol consumption for the UK (Customs and Excise figures do not disaggregate for the constituent countries of the UK): this relationship is explored in greater depth in Chapter Three. Rates in England and Wales in 1976-78 were 7.3 and 4.9 per 100,000 for men and women respectively (OPCS/Cancer Research Campaign, 1981).

TABLE 2

OESOPHAGEAL CANCER: WALES: CHANGES IN RANK ORDER OF COUNTIES BY SMR* OVER TWO PERIODS:
1950-55 AND 1958-63

MALES	FEMALES			
	1950-55	1958-63	1950-55	1958-63
Caernarvon	153 n [#]	Cardigan 156 s	Cardigan 280 m	Caernarvon 281 n
Cardigan	139 m	Brecon 152 m/s	Merioneth 274 n	Cardigan 220 s
Denbigh	133 n	Merioneth 148 n	Anglesey 260 n	Anglesey 210 n
Merioneth	129 n	Cardigan 132 m	Cardigan 246 s	Merioneth 210 n
Flint	124 n	Denbigh 128 n	Brecon 219 m/s	Cardigan 182 m

Glamorgan	118 s	Montgomery 125 m	Pembroke 212 s	Brecon 180 m/s
Montgomery	109 m	Flint 123 n	Montgomery 190 m	Flint 174 n
Monmouth	109 s	Glamorgan 122 s	Caernarvon 169 n	Denbigh 171 n
Anglesey	107 n	Caernarvon 119 n	Glamorgan 136 s	Montgomery 161 m
Brecon	95 m/s	Anglesey 105 n	Denbigh 125 n	Glamorgan 143 s
Cardigan	79 s	Pembroke 103 s	Monmouth 111 s	Monmouth 118 s
Pembroke	79 s	Monmouth 92 s	Flint 97 n	Pembroke 112 s
Radnor	75 m	Radnor 70 m	Radnor 94 m	Radnor 100 m

*Standardised on population of England and Wales # n=north m=mid s=south

Sources: 1950-55 data are from Stocks (1961) 1958-63 data are from Ashley (1969)

No particular pattern may be discerned in the spatial distribution of oesophageal cancer in England: the Merseyside conurbation, Plymouth and parts of Cumbria, Yorkshire, north Kent, East London and Cornwall have rates significantly above normal, but there are no very large clusters and no obvious geographic gradient (Gardner et al, 1983). A stronger pattern can be seen in Wales, though even this is subject to variation over time (see below).

Rates approximately twice the national average have been reported over a number of years from various parts of Wales (Stocks, 1961; Millar, 1961; Ashley, 1969) and the recent maps of Gardner et al (1983) confirm the continuing existence of pockets of significantly high mortality in Wales. More than twenty years separate the studies of Stocks and Millar (see above) and the atlas of Gardner et al (op cit). If the data compiled by these authors is compared it becomes apparent that rates in both sexes are subject to considerable variation over time, and that the rank ordering of areas by their SMRs may change over quite short periods: this, however, is not surprising in small populations. Table 2 (see facing page) ranks male and female oesophageal cancer SMRs in the 13 pre-1974 Welsh counties: the data are for two narrowly separated periods: 1950-55 and 1958-63. Taking each time period separately it can be seen that there is little correspondence between the sexes, confirming the visual impression given by the maps of Gardner et al (op cit) that the spatial correspondence between male and female high-mortality areas is very slight. The rank ordering of Welsh areas also changes:

almost completely in the case of male SMRs ($r = .28$). Only the female areas show some continuity over time ($r = .59$). If, however, the counties are classified according to their geographic position in Wales (i.e. North-, Mid- and South Wales), it appears that there is a marked north-south gradient. Taking the five counties with the highest SMRs in each column (Table 2), northern counties make up 50% of the total, mid-Welsh counties 33% and southern Welsh counties 17%.

The strong north-south mortality gradient in Wales led Ashley (1961) to postulate a racial (and, by implication, genetic) component to the disease. Classifying males (females may marry and change their surname) according to English or Welsh surname, and combining this information with data on the proportion of Welsh speakers by area, Ashley divided Wales into 'high', 'intermediate' and 'low' zones, denoting the degree of 'Welshness' of the population. There are marked north-south gradients in both the proportion of Welsh speakers in the population and in the proportion of people with Welsh surnames. Using his index of 'Welshness', Ashley calculated that the proportion of Welsh to non-Welsh in Wales ranged from 84%-16% in Anglesey, to 35%-65% in Glamorgan and 20%-80% in Radnor. The gradient in oesophageal cancer, particularly for women, corresponds very well with the gradient of Welshness:

TABLE 3: Oesophageal cancer SMRs* in Wales, 1958-63,
by sex and zone of Welshness

Zone	Male SMR	Female SMR
High Welsh	134	226
Intermediate Welsh	119	163
Low Welsh	101	124

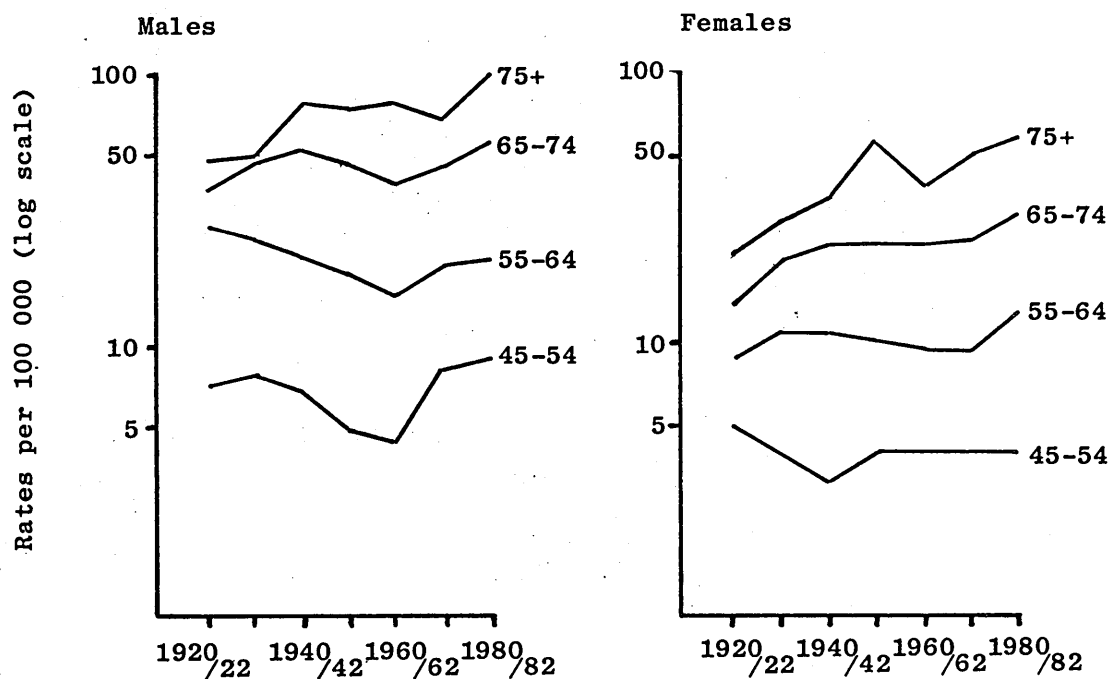
* Standardised on population of England and Wales.

Source: Adapted from Ashley (1961).

Ashley noted that the range of SMRs for non-Welsh inhabitants of Wales corresponded closely with the range in England itself, while SMRs of the Welsh in Wales were significantly higher in both sexes. Between 1958 and 1963 SMRs in the Standard regions of England ranged from 86-114 for men and 80-118 for women. In Welsh local authority areas SMRs ranged from 70-156 for men and from 100-282 for women. Ashley computed the relative risk (i.e. Welsh against non-Welsh in Wales) of contracting cancer of the oesophagus as 1.51 for men and 2.42 for women. Ashley speculated that the much higher SMRs and relative risk of Welsh women in Wales may be related to differences in immunological capacity, and that these differences may be carried on the X chromosomes of the women in this small (and arguably racially distinctive) gene pool.

Elsewhere, the role of inheritance in oesophageal cancer has been largely discounted (section 1.1.3), nor is it absolutely necessary to posit a genetic factor to explain the greater frequency of iron

FIGURE 1: OESOPHAGEAL CANCER IN SCOTLAND: AGE-SPECIFIC DEATH RATES
1920-22 / 1980-82



Source: Annual Reports of the Registrar General for Scotland

deficiency anaemia and Plummer-Vinson syndrome among Welsh women (see section 2.3.3). Another hypothesis which has been used in attempts to explain the oesophageal cancer pattern in Wales concerns the distribution of heavy metals in surface deposits and water supplies: this hypothesis is explored in Chapter Five.

1.5.4 Scotland

Analysing patterns of oesophageal cancer mortality in Scotland is the main purpose of this work: aspects such as spatial distribution, occupational mortality, drinking and smoking habits are therefore dealt with at length in subsequent chapters. In this section remarks are confined to brief descriptions of time trends and current rates for the disease in Scotland.

In Figure 1 (opposite) each of the male curves shows that rates dipped around 1960-70, to be followed by a more or less steep rise. However, it is not possible to say with certainty whether the pattern is the outcome of a cohort effect, or was caused by a particular historical event (a rise in alcohol consumption consequent upon a fall in real prices might be a relevant example). Part of the reason for the uncertainty lies in the nature of the Scottish statistics. OPCS³ publishes data for England and Wales by consecutive five-year periods and gives rates by five-year age groups. The relatively large numbers involved minimise the effects of random fluctuations on the rates, while the use of five-year age groups makes it easier to pinpoint the years when changes in cohort mortality occur. By contrast, the published Scottish data (Annual Reports of the Registrar General for Scotland) are based upon three-year periods at the beginning of each

3. Office of Population Censuses and Surveys, London

decade, while the published rates are for ten-year age groups only. decade, while the published rates are for ten-year age groups only. The shorter data periods and the small overall numbers create a suspicion of unstable rates, while the publication of rates by ten-year age group considerably coarsens the picture. With these caveats in mind, it nevertheless appears that from 1920-1960 there was an overall decline in oesophageal cancer mortality among Scottish men in age group 45-69. From 1960 rates in all male age groups began to rise, steeply in the 75+ age group (rates for the 75+ group have risen throughout the century, except for a slight dip around 1970). For women the impression is of an overall rise since the 1920s: only the 45-54 age group moves in contrary fashion, but with such low rates for this age group the movement may be no more than a chance fluctuation. The dip in female rates in the 75+ age group (around 1960) is similar to that for men of the same age, but occurs ten years earlier. Age-adjusted death rates for Scotland have risen from a 1960s low of 7/100 000 per annum for men, to 12/100 000 per annum in 1980-82 (women 5 - 9/100 000 over the same period) (Registrar General for Scotland, 1971 and 1982).

CHAPTER TWO: THE SEARCH FOR AETIOLOGICAL AGENTS: DIET

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CHAPTER TWO: THE SEARCH FOR AETIOLOGICAL AGENTS: DIET

2. Introduction

In broad terms, diet appears to influence the development of oesophageal cancer in two ways:

- 1) deficiencies of vitamins, minerals and perhaps protein may predispose the body in various ways to carcinogenic attack;
- 2) the diet may also supply the carcinogenic agent, although tobacco and/or industrial carcinogens may be equally responsible.

In some cases a deficiency may occur which causes both the presumptive carcinogen and the body's impaired response to its attack; a soil/plant zinc deficiency is one example discussed here in section 2.3.1. A third, and perhaps locally significant aspect of diet in oesophageal cancer is the possibility of mechanical trauma. The potential for silica or other mineral particles to damage the intestinal mucosa and to provide 'anchorage' for carcinogenesis is discussed in section 2.2.2. A few items, such as opium dross in Iran, herbal emetics in Transkei and herbal cathartics in Curacao, have been linked to oesophageal cancer in those specific areas; they are mentioned only in passing. This review will concentrate, for the most part, on factors which could conceivably affect the development of oesophageal cancer in Europe generally and Scotland in particular.

Deficiency conditions pose problems of classification in a study principally concerned with cancer in Europe. In impoverished populations nutritional deficiencies arise as a direct consequence of food shortages or lack of money to buy food. In poor countries, lack of purchasing power also means that food cannot be imported, nor may factors limiting food production (e.g. lack of fertilizers and/or trace element imbalance) be alleviated. This in turn means that such populations are forced, if food aid is excluded, to live off the food they can produce from their own land, however defective the food may be in quality, or limited in quantity. Although unfortunate, even tragic, for the populations concerned, such conditions should, in theory, simplify the search for aetiological factors; soil conditions, crop quality and storage conditions can all be monitored directly and in the knowledge that what is being measured thus is also being consumed by the study population.

In the affluent nations locational and dietary factors are seldom closely related. Armstrong (1962) has drawn attention to the problems of relating dietary intake to geographical location in Europe, where the volume of cross-border traffic in food is enormous and where only a tiny minority of people eat food they have grown themselves or which was even produced locally. Moreover, in northern Europe at any rate, nutrient deficiencies arising from inadequate intake are rare. Deficiency symptoms do occur in certain well-defined groups (discussed in sections 2.3.2-2.3.5), the most important of which is that of the chronic heavy drinker. Deficiency symptoms are not infrequently seen in heavy drinkers, even when the individuals

concerned have what would normally be considered an adequate diet. In such instances nutrient deficiencies relate not to poor intake but to alcohol-impaired uptake and metabolism of nutrients. Avitaminoses are common in heavy drinkers and, in the context of this study, are more appropriately discussed in the section dealing with the effects of alcohol, rather than that which deals with purely dietary risk factors.

The material reviewed is ordered as follows: sections 2.1.0-2.1.3 and 2.1.7 deal with those dietary carcinogens thought to be associated specifically with cancer of the oesophagus. In section 2.1.4, data on cancers of the stomach and oesophagus are used as the basis for a discussion of dietary carcinogens and the important matter of organ specificity. The putative role of salt is discussed in section 2.1.6. Bracken, as an environmental carcinogen, rather than an item of diet, is considered in section 2.2.4. Mechanical and thermal trauma of the oesophagus are dealt with in sections 2.2.2-2.2.3. Zinc deficiency is discussed in sections 2.3.1-2.3.2 and a review of iron deficiency leads to a consideration of anaemia and Plummer-Vinson syndrome. The chapter on diet finishes with an account of the dietary data publicly available in the UK, and also touches briefly on the limitations of dietary surveys in cancer research.

2.1 Dietary carcinogens

2.1.1 Nitrates, Nitrites and Nitrosamines

Nitrates

In themselves, nitrates are not carcinogenic; they are of interest to oncologists, however, as precursors of nitrites and nitrosamines. High levels of nitrates in green vegetables are commonly the result of excessive N-fertilizer use. Similarly, nitrates in drinking water are generally the result of N-fertilizer run-off from agricultural land (but may also occur naturally from rainwater leaching of organic material). According to Culliton and Waterfall (leading article, 1978), in the USA 80% of the nitrites that reach the stomach are formed in saliva from the nitrates that occur naturally in vegetables, water and soil, and that are enhanced by intensive N-fertilizer use. Plants grown in molybdenum- and zinc-deficient soils show raised nitrate levels in their leaves (Burrell et al, 1966, and Fong, review, 1982). In this context, soil-zinc deficiency may be doubly significant for oncogenesis since, as Fong (1982) points out, the deficiency which promotes development of carcinogens or their precursors in plants also reduces the effectiveness of the body's protective response to those same carcinogens.

Nitrites

Under conditions of drought nitrates may be converted to nitrites in the growing plant, even at normal nitrogen supply levels (Schuphan, 1965). Nitrates may also be converted to nitrites in harvested green

vegetables (notably spinach, but also other members of the Chenopodiaceae (goosefoots) and Brassicaceae (cabbages)) under warm storage conditions and particularly after a freeze-thawing sequence (Wagner and Borneff, 1967). Nitrates from both green vegetables and drinking water may be converted to nitrites and nitrosamines by the action of bacteria in the mammalian gut (Spiegelhalder et al, 1976; Tannenbaum, 1976). Nitrites were not suspected of being directly carcinogenic until work by Newborn et al (cited but not referenced in Culliton and Waterfall, 1978) showed a tentative link between nitrites and the development of lymphomas and lymphoreticular sarcomas in rats; as yet, however, there is nothing positive to link nitrites directly with squamous-cell carcinomas. Nitrites are still chiefly of concern to oncologists as precursors of nitrosamines.

Nitrosamines

The role of nitrosamines in animal carcinogenesis is beyond doubt, but although they occur in food, drink, tobacco- and woodsmoke, there is still no conclusive evidence that they are carcinogenic to humans. The circumstantial evidence, however, must be regarded as strong: over 50 nitrosamines have been described which are carcinogenic in a wide range of animal species including sub-human primates; they induce tumours in many different tissues, sometimes after single or small doses, some nitroso compounds act as transplacental carcinogens, they may also act synergistically with other known carcinogens (Carter and Symington, 1975). The US Government was among the first to act

upon the inferences drawn from animal studies and regulate nitrite levels in foods: 'The discovery of nitrosamines in crisply-cooked bacon raised the likelihood that high heat was producing the nitrite-amine combination before the bacon was ever eaten, so the Government reduced the amount of nitrite that could be added to bacon or poultry.' (Culliton and Waterfall, op cit). (There may be carcinogens in burnt or browned meats other than nitrosamines. Sugimura and Sato (1983) found a number of burnt-food products that were carcinogenic to rats. Nor were pyrolysed amino acids the only presumptive carcinogens; pyrolysed hydrocarbons (e.g. caramelised sugar) also yielded suspected carcinogens (reviewed in Ames, 1983).

Animal studies have shown that individual nitrosamines display a marked tendency to target on specific organs (organotropism): examples are the production of bladder cancer by dibutyl nitrosamine and oesophageal cancer by N-nitrosomethylene and N-nitrosopiperidine (Fong, review, 1982). According to Fong (op cit), N-nitrosamines are actually precarcinogens and give rise to the real carcinogens (possibly carbonium ions) only after enzymatic action in the body. These highly reactive substances - in addition to the free oxygen radicals discussed by Ames (1983) - then interact with DNA and RNA, resulting in the initiation of carcinogenesis.

At first, nitrosamines seemed to provide a promising lead in investigations of oesophageal cancer. Cook-Mozaffari (1980) writes:

'Nitrosamines appear repeatedly in studies of cancer of the oesophagus. Not only are they strongly carcinogenic but they are also the only group of chemicals which give rise to oesophageal tumours in experimental animals.' (Emphasis added.) Epidemiological studies, however, have so far failed to provide the strong, positive link with cancer of the oesophagus. Earlier reports that nitrosamines had been detected in grain-based spirits from a high-incidence oesophageal cancer area of Zambia (McGlashan et al, 1968) were subsequently discounted after more refined analytical techniques had been developed (Collis et al, 1971; Gough, 1977). However, studies from widely separated areas (e.g. America, South Africa, Iran, Northern China and France) have reported nitrosamine contamination of food and drink, generally at or below the level of 5µg per kilo of food or litre of beverage (Cook-Mozaffari, 1979). Goff (1979) reported low levels of dimethylnitrosamine (typically less than 10 ppb) in American and European beers and in Scotch whisky, giving rise to 'scare' reports in the British press (references and follow-up discussions in the next section). Since these low levels of nitrosamines have been reported in so many studies from both high- and low-incidence areas, Cook-Mozaffari (1980) concludes that there is probably a general background level of contamination, of little significance for cancer of the oesophagus. This is not to say, however, that nitrosamines are nowhere implicated in oesophageal cancer. In China, 'pickled' (or, more accurately, rotted) vegetables and mouldy bread are suspect as sources of nitrosamines or their precursors (Cook-Mozaffari, 1980). Given that soil-zinc

deficiencies and high leaf-nitrate levels have been reported from the same area, given also that nitrosamine precursors, if not actual nitrosamines, can develop in nitrate-rich leaves under certain conditions, then it is reasonable to suspect that the carcinogenic agent(s) in 'pickles' may be one or more nitrosamines. However, non-nitrosamine compounds such as the lactone group of mycotoxins should not be ruled out as carcinogens in mouldy food. (Some inter-associations of fish, salt, pickles and moulds which have been noted in epidemiological studies are also discussed in sections 2.1.6 and 2.1.7).

2.1.2 Nitrosamines in the Scottish diet

In 1979 there were press reports that nitrosamines had been detected in some brands of Scotch whisky ('Cancer risk for Scotch drinkers' - Daily Telegraph, 9.8.79; 'Cancer risk found in Scotch whisky brands' - Financial Times, 9.8.79). The amounts, however, were minute, reportedly 'up to 2 parts per 1000 million.' It also emerged that the defective malting process which had given rise to the nitrosamines had affected only a few brands of whisky, had been used for only three years and was now discontinued (Wilkinson, PC - 1979). Even if similarly defective malting methods had been commonplace in the two or three decades preceding the study period (and it is not suggested that they were), it is scarcely conceivable that the very small amounts of nitrosamines from this source could have had much bearing on the development of oesophageal cancer in Scotland.

A more significant source of nitrosamines in the Scottish diet may be cured meats and fish. Smoke- and brine-cured meats were formerly an important part of the Scots diet (Walker, 1981) and even now consumption of sausages, ham and bacon are somewhat higher than in England and Wales (figures below). Similarly, cured fish has a long history in Scotland, from smoked salmon at one of the scale to Arbroath 'smokies' and 'finnan haddie' at the other end. In 1980, total consumption of smoked or brined meat and fish in Scotland averaged 14.5 kg per head per year, compared with 13.1 kg per head per year in England and Wales (National Food Survey, 1980).

The author's attempt to focus on regional consumption levels of specific food items (e.g. bacon, ham, smoked fish, etc.) failed for lack of published data. A lengthy search through nutrition abstract journals and journals dedicated to Scottish health problems (e.g. Health Bulletin) found no article concerned with food consumption levels in Scotland generally, nor any dealing with regional variations in consumption of particular food items. University departments, domestic science colleges and Area Health Authorities were canvassed in hopes of locating unpublished data: no positive replies were received. The Institute of Physiology at Glasgow University are 'certain' that no dietary surveys exist. (J.G.V.A. Dumin, Department of Physiology, University of Glasgow, personal communication, 1984).

This leaves the 'National Food Survey' as the only general source of information on the Scottish diet. The National Food Survey is discussed below in section 2.5.1. Not only are there apparently no published data on regional consumption patterns within Scotland, it appears that little if anything is known about regional variations in methods of food preparation. This is an important consideration where the concern is with levels of nitrosamines in the diet. For example, pre-soaking, followed by boiling of cured meat - with several changes of water throughout - may be expected to reduce nitrite/nitrosamine levels, whereas frying or roasting may result in concentration or manufacture of these substances.

The existence of a population with a known high consumption of preserved foods (and hence, it could be assumed, with a high exposure to nitrites and nitrosamines) would provide a useful basis for testing the hypothesis that nitrosamines may be involved in human oesophageal cancer. If such a population were to show low rates for oesophageal cancer, this would tend to confirm the conclusion (quoted earlier) of Cook-Mozaffari (1980) that these substances are, after all, of little significance in the aetiology of this particular cancer. Scottish data, alas, do not permit any conclusions to be drawn in the matter, one way or the other. Average per capita consumption of smoked and brined meat and fish is slightly higher in Scotland (10.7% in 1980) than in England and Wales, and oesophageal cancer rates are broadly double those of England and Wales. The absence of regional food consumption data

from within Scotland, however, makes it impossible to correlate consumption of individual food items with regional variations in mortality rates.

(For more than 20 years the vast majority of 'smoked' fish in Scotland has not been smoked at all but treated with commercial smoke-flavour essences (Waterman, PC, 1984); only the more expensive fish such as salmon are still cured in actual smoke. While the carcinogenic component(s) of fish flavoured with essences may have been greatly reduced, they may not yet have been completely eliminated. Pool et al (1983) sound a note of caution: smoke essences are prepared from smokehouse smoke by condensation and purification and, according to the authors, '...genotoxic components may be present in the brown-colour fractions of smoke aroma essences, but further study is needed.')

The population of one European country - Iceland - has a remarkably high intake of salted and smoked foods and is also noted for its high rates of stomach cancer (crude annual rate for males 1957-1960: 60.8/100 000: male/female ratio 1.8 (Armstrong, 1963)). Surprisingly, in view of the apparently high consumption of dietary¹ nitrosamines, oesophageal cancer rates are rather low (see page 47). The case of Iceland is of considerable interest to anyone wishing to distinguish between factors leading to stomach cancer and those giving rise to cancer of the oesophagus.

1. As distinct from nitrosamines in tobacco smoke (Rhoades & Johnson, 1972).

2.1.3 Iceland - nitrosamines in smoked and salted foods

Historically, the search for causal factors which might explain the high incidence of stomach cancer in Iceland has centred on trace-element deficiencies in the soil and diet (Armstrong, 1963) and on the polycyclic hydrocarbon content of smoked food (Bailey & Dungal, 1958; Dungal, 1961). Of these two hypotheses, a carcinogenic component in smoked foods was the more convincing and this line of enquiry was also pursued by Shabad (1961) in villages along the Baltic coast of Latvia, where smoked fish was a daily item of diet and stomach cancer rates were high. Later research, however, suggested that smoked meat and fish also contain appreciable amounts of nitrosamines, as well as carcinogenic hydrocarbons (Fazio, 1971; Wasserman, 1972). Salted but unsmoked fish have also been shown to contain nitrosamines (Fong & Walsh, 1971; Fong & Chan, 1973), presumably from the saltpetre added to the salt used for curing. However, these last two studies relate to salted fish in the Chinese diet and curing methods may not be the same as in European countries.

The traditional diet of Iceland is almost certainly unique in the 'Western' world: probably no other group consumes so much salted and smoked food as the Icelanders, even today. Bailey and Dungal (1958), Dungal (1961) and Armstrong (1963) all confirm the earlier

findings of Sigurjonsson (1943) that the Icelandic diet is simple and in most rural areas had remained the same for the past 60 years. Sigurjonsson (1943) found that nearly 60% of daily energy intake was provided by fish, mutton and milk products, and that these foods, along with potatoes, were the main dietary staples. Armstrong (1963) noted that the only fresh meat eaten on farms was at slaughter time in Autumn; for the rest of the year all meat was either salted, smoked or - a recent introduction at the time - frozen. Practically no fresh vegetables were eaten and only small amounts of dried fruits such as prunes, apricots and raisins. In Reykjavik canned, processed and fresh fruits were available, but their high cost limited purchases. In rural areas Armstrong found that fresh fruits were mostly ignored, not only because they were expensive but because people had no taste for them. A recently returned traveller reports that, although improved transport and food technology have brought a varied diet within reach of most Icelanders, they still cling to tradition:

'Icelandic diet is traditional and monotonous... even in Reykjavik most people were brought up on farms, or their parents were, and their dietary inclinations remain much the same as those of the people in rural areas still. There were no vegetables except potatoes, turnips and cabbage, the two latter vegetables eaten only once a fortnight. Meat and fish, the meat mostly mutton but some horse flesh, were eaten boiled fresh, or smoked.

'Salted or smoked meats were eaten about twice a week even in Summer, when fresh meat and fish were available, so that the amount probably increased in Winter.'

(L.M. Sturgis, New College, Oxford, personal communication, 1984)

The extent to which preserved foods were eaten in the rural areas 20 years ago is astonishing. Armstrong (op cit) found that 70% of farms smoked their own meat and that salted meat was a main item of diet in all farms surveyed. In one area Bailey and Dungal (1958) found that smoked trout was a daily item of diet for eight months of the year. It may be that, in countries where smoking and salting are common methods of preserving food, both nitrosamines and polycyclic hydrocarbons are implicated in carcinogenesis and may even interact synergistically. Bailey and Dungal (op cit), however, only looked for polycyclic hydrocarbons and, of the many they found, only one (3:4 benzpyrene) was strongly carcinogenic; this was found, however, in large quantities. Average samples of smoked trout yielded 2.1 µg benzpyrene per 1000g wet material which, say the authors, 'was comparable to the amount of 3:4 benzpyrene in the mainstream from 250 cigarettes.' Given that smoked foods are daily fare in some rural areas, the consequent intake of carcinogenic hydrocarbons would - argue the authors - be sufficient to explain the high incidence of stomach cancer. (In fact, as with lung cancer, the association of stomach cancer with smoke carcinogens raises as many questions as it appears to 'solve'. Why, for example, if smoked fish contains such high concentrations of 3:4

benzpyrene do so many people in Iceland not get stomach cancer? Measurement of vitamin levels, in particular the A group, might provide some answers.)

TABLE 4 Iceland: Crude death rates per 100,000 population for three cancers. Data for the period 1957-1960

ICD No.	Cause	Males	Females
150	oesophagus	8.4	5.6
151	stomach	60.8	33.0
152	colon	7.9	8.9

Source: Armstrong (1963)

Armstrong (op cit) regards the above rates for cancers of the oesophagus and colon as 'fairly high', although he acknowledges that the rates are based on very few deaths and are, in[∇]consequence, very unstable. In fact, at one point (1939) in a 41-year series, the male rate for oesophageal cancer fell to 4.0/100 000, and the female rate to 3.8/100 000. Cook-Mozaffari (1980) gives a more recent annual incidence rate for cancer of the oesophagus in Icelandic males aged 35-64 years as 3.4/100 000 (data from Waterhouse et al, 1976). For comparison, the annual death rate for cancer of the oesophagus in Scottish males aged 35-64 years during the period 1970-1974 was 9.4/100 000 (rate derived from data supplied by the Registrar General for Scotland).

It is apparent that the Icelandic diet described by Dungel, Armstrong and other writers is very deficient in vitamin C for much of the year, so that the prophylactic effects of this vitamin would have been largely absent. Fresh fish and fresh-killed meat provide small amounts of vitamin C (Fisher and Bender, 1975) for Icelanders at certain times of the year, but possibly the only continuous source of this vitamin in the diet of former times was the residue left in potatoes after cooking. However, it should be said that, in the absence of actual carcinogens, even frank vitamin deficiencies can exist without cancer emerging. Yang et al (1982) investigated plasma retinol, riboflavin and ascorbate levels in two Chinese population groups, one in the high-risk area of Linxian, the other in the low-risk area of Fanxian. Widespread deficiencies of vitamin C and riboflavin were found in both areas: it emerged that the nutritional status of those tested in the high-risk area was no worse than that of the people tested in the low-risk area.

2.1.4 Dietary carcinogens and organ specificity: stomach versus oesophagus

What the case of Iceland clearly shows is that although nitrosamines and polycyclic hydrocarbons may be carcinogenic in the oesophagus, the site most affected is the stomach. This accords with expectation, in that the stomach is in contact with food for hours, rather than seconds, as in the oesophagus. Moreover, although not an organ of absorption (other than for water and alcohol), the highly convoluted gastric mucosa form a huge surface area susceptible to

penetration by carcinogenic molecules. Since carcinogens remain in contact with the stomach lining for longer periods and in larger quantities than in the oesophagus, it might be expected that stomach cancer would have a shorter development period than oesophageal cancer, and thus earlier onset. Thus it proves in Iceland, where stomach cancer typically presents in the fifth and sixth decade (though the disease is not infrequent among men in their forties): the onset of oesophageal cancer usually occurs in the sixth or seventh decade (Armstrong, 1963).

The marked disparity in degrees of exposure to carcinogens at the two sites (stomach and oesophagus) would seem to create a major stumbling block to acceptance of dietary nitrosamines and hydrocarbons (as distinct from those contained in tobacco smoke) as an important factor in oesophageal cancer. If dietary nitrosamines were involved in oesophageal cancer we might expect that anyone presenting with that condition would also have stomach cancer, on grounds that the stomach would have had by far the greater exposure. By the same reasoning, if nitrosamines from food were involved in carcinogenesis at both sites, then, even taking into account the different ages of onset, autopsies of stomach cancer victims should more often yield evidence of precancerous changes in the oesophagus (e.g. dys-, hyper- or parakeratosis, hyperplasia or lesions, etc.). While multiple tumours within the oesophagus or at the other head and neck sites are not uncommon (e.g. Suckow et al, 1961; Berelowitz and Kaye, 1965), simultaneous tumours at the oesophagus and other sites

(not head and neck) are mentioned only rarely. Of 109 oesophageal cancer cases autopsied by Giarelli et al (1982), ten had tumours at other sites, of which only two were carcinomas of the stomach. There is of course the possibility, albeit slight, that such cases are not so rare, merely that they are not identified. Crossfill (1973) describes a number of ways in which cancers may escape inclusion in the Cancer Register: how, for example, an autopsy performed with the aim of verifying a particular diagnosis may miss an unlooked-for condition also present. If dietary nitrosamines are involved in oesophageal cancer, then only extreme organ specificity on the part of the carcinogen involved would account for someone developing oesophageal cancer but remaining free of stomach cancer. For this to occur it would be necessary to postulate some fundamental difference at the cellular (or even molecular) level between gastric and oesophageal epithelium. Such a difference may well exist but, if so, the author has encountered no reference to it in the epidemiological literature.

2.1.5 Caveat

Having discussed at some length the possible roles of nitrosamines and polycyclic hydrocarbons in the aetiology of oesophageal cancer in Iceland (and, to a lesser extent, in Scotland), the possibility must be admitted that the populations of the two countries actually consume less nitrites and nitrosamines than do people in England and Wales. Ames (1983) mentions that beets, celery, lettuce, spinach,

radishes and rhubarb (all commonly-eaten vegetables in England and Wales) all contain about 200 mg nitrate per 100 g portion and that beets (whether roots or tops is not specified) tend to enhance carcinogenesis. Cabbage, on the other hand, appears to contain carcinogen inhibitors - perhaps large amounts of vitamin A (Tucker, review, 1979). The American finding that 80% of dietary nitrates come from green vegetables and drinking water¹ has already been mentioned. Present day Scottish diet is appreciably poorer in fresh vegetables and fruit than that of England and Wales (National Food Survey), while Icelanders, at least in rural areas, consume almost no green vegetables, even now.

If it is true for the UK, as it is for the USA, that the majority of dietary N-compounds derive from green vegetables and drinking water, then it is the English and Welsh, with their higher consumption of fruit and vegetables and larger areas of fertilized farmland, who would ingest the most N-compounds. Only detailed dietary surveys which include analyses of nitrite/nitrosamine levels in food samples could clear up this point. James (1978) draws attention to the fact that, as vegetable intakes rise, vitamin C intake increases, but so also does intake of nitrate: he points out that more work is needed to find out which is the more dominant influence on carcinogenesis, the N-compound cancer promoters, or the vitamin cancer inhibitors.²

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1. Chilvers et al (1984), in a study of nitrate levels among well-water users in East Anglia, found that where the waterborne nitrate level was less than 50mg/l (the World Health Organisation recommended level), 30% of ingested nitrate was from water.
 2. After completion of the main text the author's attention was drawn to a study by Forman et al (1983) of salivary nitrate levels in Oxford and the north of England. Salivary nitrate levels were found to reflect consumption of green vegetables but to be inversely related to stomach cancer rates: the inference was that the link between nitrates and stomach cancer is weak (reported in Gardner, 1984).

On the last point raised above, Ames (1984) has reviewed the evidence for the role of anticarcinogens in the diet, of which vitamin A (beta-carotene) and vitamins C and E are probably the most important. (Not all anticarcinogens are vitamins, two others of importance are the element Selenium and glutathione, a tripeptide.) Vitamins A, C and E are known to remove free oxygen radicals from tissues and prevent lipid peroxidation (free oxygen radicals are implicated in DNA defects, lipid peroxidation in ageing). Adequate dietary supplies of anticarcinogens may give protection when known carcinogens are present; conversely, the presence of certain types of cancer may signal a lack of dietary anticarcinogens, rather than particularly high levels of specific carcinogens.

2.1.6 Salt

Nagai et al (1982) found an association between Japanese pickled vegetables (which often contain salt) and stomach cancer, also an association between salted and dried fish and oesophageal cancer. Tuyns (1982) also noted an association between levels of salt consumption and cancers of the oesophagus, stomach and colon in France. After adjusting for alcohol consumption, however, Tuyns felt able to assert that salt is not aetiologically important and that the apparent role of salt is due to the relationship between salty foods and alcohol drunk to quench the resulting thirst (Tuyns, 1983). At least one piece of rat work lends support to Tuyns' conclusions: in an early experiment to test the relative carcinogenicity of smoked and salted foods, Dungall (1961) fed one

group of rats with smoked fish, another group salted fish and the controls, standard food. At death the average weight of the rats fed on smoked fish was 20% less than the average weight of the controls; 21 out of 24 rats on smoked food died from tumours within three months; none of the rats on salted or standard food died before the experiment was concluded, nor - on sacrifice - was any found to have developed tumours. On the other hand, Fong et al (1979) recorded mutagenic activity (measured using the Ames Salmonella mutagenic assay) in urine collected from rats fed on traditional Chinese salted fish. It is possible, however, that European and Chinese methods of salting fish differ; Chinese salting involves the use of nitrates as well as sodium chloride (Fong and Walsh, 1971 ; Fong and Chan, 1973) and it is possible that the nitrosamines arise from the combination of secondary amines in the fish with the nitrate preservative.

2.1.7 Mycotoxins in mouldy food

Toxic metabolites of the mould Aspergillus flavus are a locally serious health hazard in areas where grains and nuts (especially groundnuts) are stored in warm, humid conditions; these metabolites are known generically as aflatoxins. Chemically, aflatoxins are lactones (ring compounds derived from organic hydroxyacids by the elimination of water) and lactone derivatives. As well as being potent toxins, the aflatoxins are strong carcinogens in mammals,

birds and fish, especially in early life (Butterworths, 1978) and have been implicated in human cancers of the liver (Oettlè, 1964 and McGlashan, 1982) and oesophagus (Marasus, review, 1982). Weight for weight, aflatoxins are about ten times more potent as carcinogens than dimethylnitrosamine, which in turn is about ten times more potent than the polycyclic hydrocarbons (Berg, 1975). Ames (1983) describes aflatoxin and sterigmatocystin (a related mycotoxin, also produced by the Aspergillaceae) as '...among the most potent carcinogens and mutagens known.'

An intensive search for known carcinogens in the diet of people living in Iran showed only low levels of contamination by nitrosamines, polycyclic hydrocarbons and aflatoxins, and no significant correlation with cancer of the oesophagus (Cook-Mozaffari, 1980). In China, on the other hand, pickled vegetables are considered as possibly the most important cause of oesophageal cancer in Linxian County (Fong, 1982). The fate of the now well known chickens of Linxian (BBC, 'Horizon' 1981) provided what was regarded as extremely strong evidence in support of the mouldy-food hypothesis of causation. Chickens from a cancer-free stock, and from a low-incidence area for cancer of the oesophagus in humans, contracted oesophageal and pharyngeal carcinomas after being fed on a Linxian-type diet. Chromatographic analysis revealed the presence of nitrosamines in a number of food items from Linxian, including pickled vegetables, wheat, maize and millet (Fong, 1982). Soil-molybdenum deficiency and/or mould contamination were suspected of contributing to the

nitrosamines. Rat work reported by Kaplan and Tsuchitani (1978) gave results which tallied with the observed fate of the Linxian chickens: rats fed on pickled vegetables and mouldy cereals developed epithelial hyperplasia and dysplasia in the oesophagus.

In Japan, the ubiquitous *tsukonomi* (pickles) have been found associated with cancers of the stomach and oesophagus (Haenszel et al, 1976; Nagai et al, 1982). Japanese papers make reference to the salt content of traditional pickles, but appear to ignore one obvious point of similarity with the Chinese situation: the direct association of Japanese pickles with mouldy cereals. Most traditional pickles in Japan are produced by a method which involves immersing the vegetables in brine for one or two days, then burying them in *nuka* (yeasted rice bran) for a week or more. Over time, each batch of *nuka* develops its own mould flora and a successful batch - giving a prized individual flavour to the pickles - may be kept for as long as ten years (Martin and Martin, 1970).

Nagai et al (1982) report a strong positive correlation ($p < 0.01$) between oesophageal cancer in Japanese women and consumption of soy sauce; the relationship for men is also positive but non-significant. The same authors also report that *miso* (fermented and salted soya bean paste) is strongly correlated with oesophageal cancer in Japanese men; the relationship for women being weakly positive.

Why the sexes should be differently affected is not at present known. What may be of interest, in the present context, is that both soy sauce and miso are fermented with the aid of an *Aspergillus* mould, in this instance *A. oryzae* (mentioned in Kmet, 1970). Sugimara and Sato (1983) investigated the action of nitrites on a number of foodstuffs and found that many brands of soy sauce produced a mutagen highly active towards *Salmonella typhimurium* TA100. The authors isolated two isomers of a complex carboxylic derivative² which appeared to be the direct mutagenic agents: the only brand of soy sauce examined which did not contain these substances was found to lack mutagenicity. Although mutagenic in the Ames test, soy sauce has been used in the East for centuries and is clearly not strongly carcinogenic in humans.

It may be that *A. oryzae* contains a weaker carcinogen than *A. flavus* (or contains the carcinogen in far smaller quantity) but that the carcinogenic effect shows up under conditions of heavy use or in susceptible populations. It is unlikely, even with the popularity of Chinese 'take-aways', that consumption of soy sauce will ever amount to anything significant in the UK population. However, the soy sauce/*Aspergillus* connection might perhaps be borne in mind in any future cancer surveys among UK groups of Chinese origin. A further point to consider is that miso and soy sauce are popular among vegetarians and vegans, among whom nutrient deficiencies have

2. 1-methyl-1,2,3,4-tetrahydro-3-carboline-3-carboxylic acid.

been detected in the past (see section 2.3.). The combination of even a mild carcinogen with low intake of certain vitamins might be important (*vide* Ames (1984), q.v. section 2.1.5).

2.2 Agents of oesophageal trauma

2.2.1 Corrosive substances

Swallowing of lye (caustic potash solution) carries an increased risk of oesophageal cancer (Wynder and Bross, 1961); however, this particular source of trauma is largely, though not exclusively, confined to Scandinavia. Children more often ingest lye than adults and carcinoma from this type of injury develops at an earlier age (Oettlé, 1967). There is a suggestion that lye is itself carcinogenic, since carcinomas tend to develop within the scarred areas. Lye is a seasonally common item in Norwegian and Swedish kitchens, being used in the preparation of *lutefisk*, a dish widely eaten at Christmas. The association of lutefisk with festivities suggests that alcoholic impairment may perhaps have something to do with the accidental drinking of lye by adults.

2.2.2 Sharp fragments and fibres

A number of writers have drawn attention to the monotonous diets of coarse dark breads common to the high-incidence areas of the Soviet Union, Iran and China (Cook-Mozaffari, review, 1980). O'Neill et al (1982) report finding huge quantities of sharp silica fragments

in tissue samples from Chinese oesophageal cancer victims; typically 37,000 particles per gram of tissue in the cancer cases, contrasting with 3,700 particles per gram from a control group in New Cross, London. Analysis of the Chinese diet revealed no unusual concentrations of silica in wheat or maize flour; millet was another matter. A sweet cake made from millet bran and persimmon paste was formerly widely eaten in Linxian County and, although now uncommon, would have been eaten by most adults. O'Neill et al speculate that sharp silica fragments in the millet cake cause repeated trauma and/or spend some time embedded in the oesophageal mucosa; they also report that biopsy samples from the Transkei show similarly high concentrations of silica. Whether sharp fragments cause cancer by a process of repeated abrasion, as shown by Argyris and Slaga (1981) in mice, or by providing 'anchorage' around which cells may proliferate (Maroudas et al, 1973), is still not known. Plants grown on sandy soils frequently develop phytoliths, i.e., precipitated silica casts of their sap vessels. Berg (review, 1975) mentions that phytoliths are in the same size range as asbestos fibres and hence may be one more possible source of risk if ingested. The possibility that silica fragments from bracken may be implicated in some parts of the world is discussed in the following section. Massé (1976) cites an unreferenced source, implicating either smoked fish or small bony fish in high-incidence areas of Kazakhstan and Iran, but neither Mahboubi and Aramesh (1980), nor Cook-Mozaffari (1979 and 1980), mention these items.

There is some evidence linking asbestos fibres with cancer of the oesophagus (though asbestos may not be the primary carcinogen for this tumour, as it is for pleural and peritoneal mesothelioma). In a study of workers from the Natal, Bradshaw and Schonland (1969) found that their oesophageal cancer group had an excess of workers involved in lagging pipes, asbestos mining and asbestos cement manufacture. However, a major study of lung cancer mortality among North American insulation workers (reported in Selikoff and Hammond, 1975) confirmed earlier suggestions that asbestos workers who have never smoked are no more at risk of lung cancer than men not occupationally exposed to asbestos dust (Selikoff et al, 1968). In the light of the most recent surveys of smoking and drinking in South Africa (Bradshaw et al, 1983), it is likely that the increased risk of oesophageal cancer noted in South African asbestos workers is the result of tobacco and alcohol acting on tissues made susceptible by asbestos fibre, rather than asbestos being the primary carcinogen.

2.2.3 Hot drinks

Tea drunk at high temperatures has been implicated in studies from Iran, the Soviet Union and China. Mahboubi and Aramesh (1980) report that both tea use per individual and the temperature at which the tea is drunk is higher among the high-risk Turkoman population than among other groups in Iran. In an early study, Kwan (1937)

believed that hot tea was not involved in oesophageal cancer in China, as both men and women drank tea at the same temperature (although, in point of fact, the M/F oesophageal cancer ratio in Chinese high-incidence areas is not so pronounced (e.g. M/F ratio 1.57 in Linxian in 1980 (Yang et al, 1982) as to give this observation very much weight). In Japan, Hirayama (1955) found the death rate from oesophageal cancer in Wakayama Prefecture to be 2-3 times higher than in the rest of the country; this he ascribed to the drinking of hot rice gruel. However, the same author, working in the same province, later found a strong association with eating bracken shoots, with a particularly high risk observed when hot gruel and bracken were consumed together (Hirayama et al, 1975). Cook-Mozaffari (1979 and 1980) regards the consumption of hot drinks as serving to heighten susceptibility to carcinogenic onslaught, rather than being of primary carcinogenic importance by itself.

2.2.4 Bracken shoots and bracken decomposition products

Fong (review, 1982) notes that bracken (*Pteridium* sp.) can induce tumours in mammals and some birds and that it is strongly carcinogenic in the urinary bladder and intestine. Hirayama (1975), in the study carried out in three Japanese prefectures, found evidence suggesting that eating bracken shoots carries an increased risk of oesophageal cancer. Clarke and Clarke (1975), in a standard text-

book of veterinary toxicology, state that the toxin(s) and carcinogen(s) have not been identified; nor can it be ruled out that the several effects may be produced by one substance. Fong (op cit) also writes that the carcinogen in bracken has not yet been identified. Berg (1975), however, states that at least one of the carcinogenic agents has been shown to be shikimic acid (3,4,5-trihydroxyl-1-cyclohexene-1-carboxylic acid) and, moreover, that this acid is widespread in plants. Clarke and Clarke (op cit) list five harmful - though imperfectly understood - agents in bracken:

1. A cyanogenic glycoside.
2. A thiaminase.
3. An 'aplastic anaemia factor'.
4. A factor causing haematuria.
5. A carcinogen.

The first factor causes sudden death in animals fed on young fronds, probably due to hydrocyanic acid. Presumably the hydrocyanic acid is either destroyed or dissolved out when the fronds are cooked for human consumption. The second factor destroys vitamin B₁ in non-ruminants. Factors 3, 4 and 5 give rise to a number of syndromes in domestic animals, including depression of bone-marrow activity - leading to leucopaenia and thrombocytopaenia - and defective blood clotting, with petechial or massive haemorrhaging at many sites. Significantly, after long-term feeding, the carcinogenic agents produce neoplasms in the bladder and *intestinal mucosa*

in cattle (Pamucku et al, 1967). Rats fed on a diet of 34% dried bracken all developed adenocarcinoma of the intestinal mucosa (Evans and Mason, 1965). In the same experiment Evans and Mason controlled for any possible toxic effect of thiaminase-mediated vitamin B₁ deficiency by administering vitamin B₁ by injection to both experimental and control rats. In addition to its chemical toxins and carcinogens, however, it is worth pointing out that bracken is similar to the horsetails (*Equisetaceae*) in having a siliceous skeleton. The haemorrhagic stomach ailments of animals fed on bracken are, it is true, adequately explained by the anti-clotting agent, but this need not be the only factor; the symptoms are also consistent with prolonged irritation and penetration of the intestinal mucosa by minute silica particles. The structure and chemistry of bracken may mean that the plant supplies both traumatic and carcinogenic agents.

However, if silica fragments from bracken should prove to be involved in oesophageal cancer in those parts of the world where the plant is eaten, it is unlikely that they will be derived directly from the bracken ingested, which is usually picked for human consumption when only days old - probably before the siliceous skeleton has had time to develop. The association, if there is one, is likely to be more complex. Pitman (personal communication, 1984) observes that drinking water derived from water flowing over acid soils on which bracken grows often contains the decomposition products of both

rocks and plants, the latter including silica fragments from dead bracken. A sample of such fragments contained large numbers of particles whose size was of the order $3-4\mu\text{mm} \times 0.2\mu\text{mm}$; these are smaller than the particles found by O'Neill et al (1982) in oesophageal tumours excised from surgical patients in China, but may still represent a health hazard. Pitman hypothesises that people living in bracken-rich areas are exposed to a number of hazards from this plant, some direct, some indirect. The primary insult to the oesophageal mucosa may arise from sharp silica particles which get into the gut via drinking water; these particles are derived from the breakdown products of rock and of bracken. Additionally, bracken may contain actual carcinogens which act at the 'anchor-ages' where silica particles have become embedded (Maroudas, 1973), or the plant may contain a substance which depresses immunocompetence; again, this is not inconsistent with the observed effects in animals of bone-marrow damage and severe reduction in white blood cells (Evans, 1964). Of course, drinking water could not remain in the oesophagus long enough to do damage, but used in food preparation there might be enough fragments in each bolus of food to cause harm over time.

In Britain, bracken is officially listed as a poisonous plant with carcinogenic properties (MAFF, 1969), but has nevertheless been eaten in the past in country areas (though it was probably always a minority taste). Hartley (1954) even describes the method of

preparation and the characteristic taste of the plant: 'Tie in loose bundles and cook as for asparagus, only longer, and serve with melted bacon fat. They have a distinctive smokey flavour - you either like them very much or not at all.' Water run-off from acid rocks in Britain may contain bracken decomposition products. Berg (1975) surmises that the high incidence of bowel cancer in Scotland might be related to the ubiquity of bracken in forage areas, '...if not because of direct ingestion of fern by cattle, then by leaching of a carcinogenic agent from the plants and concentration in water or food.' It is doubtful, however, whether any solid decomposition particles would escape the settling and filtration measures applied to water for drinking, perhaps only rural houses with their own water supply would be affected. Of perhaps greater relevance to the UK situation is the fact that the carcinogens in bracken come through in the milk of cows which have grazed the plant (Clarke and Clarke, op cit). This could conceivably present a hazard to small-holders who keep one or two cows for their domestic milk supply.

2.3.0 Deficiency disease in the UK

Small-scale manifestations of 'non-alcoholic' nutritional deficiencies do occur in the UK but are confined, in general, to certain well-defined risk groups: e.g. rickets occurs in the children of Asian immigrants (Editorial, BNF Nutr.Bull: 14, 1975), iron-deficiency anaemia in middle-aged and elderly women and osteomalacia in elderly housebound women (Caird, 1978).

There have also been cases of nutritional deficiency in children and adults living on vegan and macrobiotic diets (Ellis and Montegriffo, 1971; MAFF, 1976). True beri beri and pellagra are occasionally seen, very rarely it is true, but then these diseases represent the near-extremity of a malnutrition continuum which begins with barely sub-optimal health and proceeds through conditions of increasing severity to severe deficiency, anorexia and death. Probably only alcoholics and the psychologically disturbed provided examples at the latter end of the continuum. (Strictly, malnutrition also includes the diseases of over-nutrition; coronary heart disease, obesity, dental caries and certain types of cancer; the 'diseases of affluence' (Blythe, review, 1976).) Cancer of the oesophagus, however, has not yet appeared in studies concerned with the effects of over-nutrition.

2.3.1 Zinc deficiency

This abbreviated account of the possible connections between zinc and cancer of the oesophagus leans heavily on the detailed review by Fong (1982). Zinc is essential to tissue formation and to a number of enzymatic processes; there are also indications that it is important in the maintenance of immuno-competence. Significantly, the tissues most affected by zinc shortage in experimental animals are those of the skin and intestinal mucosa. In zinc-deficient rats, for example, extensive lesions in the oesophagus were

reported (Diamond and Hurley, 1970), as well as disorders of keratinisation such as hyperkeratosis (hypertrophy of the stratum corneum, usually also with thickening of the underlying transitional layers) and parakeratosis (the reverse of hyperkeratosis: incomplete formation of keratin) (Diamond et al, 1971). Zinc deficiency parakeratosis has also been reported in pigs (Kernamp and Ferrin, 1953). The degree of keratinisation of the oesophagus has a crucial bearing on its permeability; Fong (1982) believes parakeratosis to be an important factor in rendering the oesophagus permeable - and therefore more susceptible - to carcinogens. Increased permeability, in conjunction with depressed immunocompetence and impaired healing ability, would all seem to favour tumour development. (In passing: evidence of abnormal keratin development in the oesophagus does not necessarily indicate the presence of zinc deficiency, a number of other factors also give rise to abnormal keratinisation (Massé, 1976).)

A number of factors affect zinc levels in the human body: soluble zinc compounds can be rendered insoluble (and therefore unavailable) by phytate in cereal bran; some diseases, e.g. tuberculosis and hepatitis, may result in increased excretion of zinc, with consequent symptoms of deficiency. Fong (op cit) cites a number of studies from Iran and China which connect high-cereal and low-protein diets, tuberculosis and liver disease, with low serum-zinc levels and a high incidence of oesophageal cancer.

Zinc-deficient experimental animals exposed to nitrosamines developed tumours faster than controls exposed to the same carcinogens but receiving adequate zinc (Fong et al, 1978). In other animal studies zinc has been shown to prolong the survival time of mice with tumours, and has inhibited the growth of new tumours (Poswillo and Cohen, 1971; Woster et al, 1975).

Zinc deficiency is known to result in high nitrate levels in plant leaves (Fong, 1980). A chain of causation can be envisaged in which soils deficient in zinc produce plants similarly deficient - but high in leaf nitrates; the plants in turn provide humans and animals with a diet deficient in zinc but high in the precursors of nitrites and nitrosamines. Thus, humans and animals eating the zinc-deficient plants are simultaneously exposed to carcinogens and deprived of an essential element in the body's defences against those carcinogens.

2.3.2 Zinc deficiency in Scotland?

The soil/plant/dietary zinc deficiency model may well be an important part of oesophageal cancer causation in the less-developed countries, where large numbers of people eat food they themselves have produced. In Scotland, however, such green vegetables as are eaten are very likely to have been imported, and even if not imported, zinc deficiency is a matter easily recognised (among

other things, it reduces yields) and dealt with by commercial growers. Moreover, zinc deficiency - as with many other types of trace-element deficiencies in plants - produces colour changes in the leaf (chlorosis), very unlikely to appeal either to shop customers or to the home grower. This does not mean that zinc deficiency may not play a part in cancer of the oesophagus in Scotland, merely that the deficiency - if it exists - has its origins elsewhere. In an otherwise impressive review, Fong omits to mention that chronic alcohol abuse can have a profound effect on zinc levels in the body (in fairness, her preoccupations are with oesophageal cancer in Asia). Zinc is essential to the formation of several enzymes concerned with the metabolism and elimination of alcohol, alcohol dehydrogenase, for example (Lieber, 1982). Several workers have noted lower levels of plasma zinc in the blood of alcoholics and in the blood of rats fed on alcohol (cited in Lieber, op cit). In alcoholics, zinc is lost through excretion (zincuria) and the more severe the physical symptoms of alcoholism (e.g. cirrhosis, ascites) the higher the rate of zinc excretion (Sullivan, 1967). With heavy alcohol consumption providing a mechanism for nutrient losses and a weakening of body defences, one need not look far to find the proximal carcinogen: tobacco. In Scotland, heavy smokers are overwhelmingly likely to be drinkers, and vice versa (Dight, 1976; Cummings et al, 1982).

2.3.3 Iron deficiency anaemia

Haemoglobin levels in the normal healthy male vary between 14-18 g per 100 ml blood, with an average of 15.8g/100 ml. Haemoglobin levels in women vary between 12-15g/100 ml, with an average of 14.8 g. For convenience, 14.8g/100 ml is taken as the standard for both sexes and haemoglobin levels are calculated as a percentage of this figure (Fisher and Bender, 1975). The World Health Organisation (1974) suggests a figure of 90% (13.5g/100 ml) as the threshold level at which the individual may be considered anaemic; on this basis about one-sixth of all women in the UK are anaemic (Fisher and Bender, 1975).

Among the nutrients required for blood formation are: protein, iron, ascorbic acid, folic acid and vitamins B₆ and B₁₂; the minute amounts of copper and manganese are also needed. There is seldom any shortage of these nutrients in the British diet, except in high-risk groups such as the elderly and chronic heavy drinkers.

Anaemia occurs when there is prolonged loss of blood, a failure of nutrient absorption (as with vitamin B₁₂ in pernicious anaemia) or a dietary shortage of one or more of the essential blood-forming nutrients over a long period. Women, because of menstrual blood loss over several years (typically 30-40 years but often longer), are the most prone to anaemia even in 'well-nourished' countries.

Injury, poisoning, ionising radiation and bone-marrow tumours may give rise to acute forms of anaemia in both sexes, but in men chronic nutritional anaemia is somewhat rare; alcoholics and other chronic heavy drinkers are perhaps the only high-risk group in which this type of anaemia is regularly found. Glatt (1972) cites evidence that alcoholics may develop anaemia because of neglect of food intake, lack of folic acid, liver disease and suppression of erythrocyte formation. Kil'diyarov (1975) cites evidence that alcohol depresses blood coagulation indices in healthy persons and chronic heavy drinkers alike (there was strong epidemiological confirmation of an anti-coagulant role for alcohol in the alcohol and coronary heart disease study by St Leger et al, 1979). Coagulation is most reduced in cases of severe intoxication and in chronic alcoholics. This factor may cause further problems by depleting iron in the body through blood loss. Glatt (1972) comments that '...the disturbed formation of platelets and of white blood cells may be an important factor in alcoholics' tendency to bruise readily and to bleed internally and in their (reduced) resistance to infections.'

Blood loss in alcoholics may accelerate an anaemic process already begun as a result of alcohol-induced malnutrition. A link between iron deficiency anaemia and pre-cancerous mucosal changes has been suspected for some time; Dolby (1973) writes: 'It would be interesting to know the prevalence of iron deficiency in the UK and its association with oral mucosal changes...how many patients with oral cancer in the UK have had chronically low serum levels?'

2.3.4 Patterson-Kelly/Plummer-Vinson syndrome (Sideropaenic dysphagia)

Patterson and Brown-Kelly (1919) described chronic dysphagia of middle-aged women and noted the typical atrophic appearance of the upper gastro-intestinal mucosa, with weblike deformities at the pharyngeal-oesophageal junction (post-cricoid webs). Brown-Kelly also noted that some of his patients had anaemia and Vinson (1922) reported that over half his dysphagia patients had haemoglobin levels of less than 60%. Waldenstrom and Kjellberg (1939) established the connection between this type of dysphagia and depleted body iron stores and coined the term (sideropaenic dysphagia). Ahlbom (1936) showed that sideropaenic dysphagia was not only associated with carcinoma of the meso- and hypopharynx, but also to the mouth, tongue and all levels of the oesophagus. Sideropaenic dysphagia was further documented as a pre-cancerous disease by Jacobson (1948) and Wynder et al (1957). In a number of their patients with intra-oral cancer, Wynder et al (1957) found glossitis, a history of brittle nails and early edentia, which led them to suggest that this might constitute a Plummer-Vinson-like syndrome. Reviewing their own data and those of other workers, Wynder and Bross (1961) describe the complete Plummer-Vinson syndrome as consisting of dysphagia, oral fissures, glossitis, hollow nails (koilonychia), brittle nails, anaemia and early edentia. They write: 'The majority of female [oesophageal cancer] patients had at least one symptom of the Plummer-Vinson syndrome, though the prevalence of this

syndrome was not as great as that for cancer of the hypopharynx.'

In this study the excess female deaths from cancer of the oesophagus in the extreme south-west of Scotland and in Perthshire were anomalous and the possibility of a 'Plummer-Vinson-like' condition might lie behind the higher female SMRs was considered. The probability of finding Plummer-Vinson syndromes in its full manifestation was thought slight: it had never surfaced in the Scottish literature before. Anaemia and early edentia were investigated instead, on the grounds that, if higher than expected incidences were found, this would lend support to a Plummer-Vinson-like interpretation of rates among women in these areas. The results of the investigations into anaemia and edentia are reported in sections 2.3.6 and 4.4.2.

According to Wynder and Bross (1961): 'The most pertinent facts known about diet and cancer of the oesophagus come from investigations of Plummer-Vinson disease. [These] suggest that a diet leading to chronic iron deficiency plus, possibly, deficiencies in vitamin B (particularly riboflavin) and vitamin C can induce cellular changes in the mouth, extrinsic larynx and oesophagus, making these tissues prone to cancer in the absence of either tobacco or alcohol.'

(Emphasis added.) However, the similarities between the types of dietary deficiencies suspected of causing Plummer-Vinson syndrome and the known dietary deficiencies of chronic heavy drinkers led Wynder and Bross to speculate that it might be the dietary status

of alcoholics, rather than any direct action of the alcohol itself, which gave rise to the observed high rates of oesophageal cancer in heavy drinkers. They (Wynder and Bross) point out that nutrient deficiencies are, in general, greater for whisky (sic) and wine drinkers, since beer at least contains some vitamins of the B complex. Finally, these authors state that '...the outstanding feature of the diet among the Swedish population in whom this incidence of cancer and the Plummer-Vinson syndrome is present, is the exceedingly low intake of fresh meat, fresh fish, green vegetables and fresh fruit.' On the other hand, the diet is relatively high in potatoes, butter, milk, cheese, porridge and herring.

Jacobs and Kilpatrick (1964) and Elwood (1964) felt that iron deficiency might not be the cause of the oesophageal lesions found in Plummer-Vinson syndrome, but were instead a secondary effect resulting from the gastritis and achlorhydria (absence of hydrochloric acid in the stomach juices) which frequently accompany the condition. Williams (1968) thought it possible that the atrophic changes in the gastric mucosa might be produced by 'a primary defect in immune tolerance.' As Warwick and Harington (1973) point out: 'The association of iron deficiency and the Plummer-Vinson syndrome is not found in populations unaffected by gastric atrophy. This is shown by the extreme rarity of the condition in East and Central Africa, despite the prevalence of iron deficiency and avitaminoses.'

These conflicting interpretations of the evidence have not yet been resolved. However, the view of iron deficiency as a sequel to Plummer-Vinson syndrome, rather than a causal factor, does not square well with the fact that, since the early 1950s a national programme of iron and vitamin supplementation has been carried out in Sweden and there has been a significant reduction in the number of cases of Plummer-Vinson syndrome, with a subsequent reduction in numbers of upper-alimentary tract cancers (Larsson et al, 1975).

Jacobs (cited in a conference report, Brit.Med.J. 31 May 1969, p.570) reported a study which attempted to determine whether nutritional deficiency was a cause or an effect of pharyngeal lesions: in the view of the present author the results could be interpreted as supporting either the conclusions of Wynder and Bross (op cit) or those of Jacobs, Kilpatrick and Elwood (op cit). The pharynx and oesophagus of 279 patients who had had a partial gastrectomy during the previous twenty years were examined clinically and histologically. The incidence of post-cricoid webs after partial gastrectomy was greater than in the control normal population or in patients with untreated duodenal ulcer. The patients with post-cricoid webs (2.9% of men, 5.3% of women in the sample) had a significantly greater degree of nutritional impairment than those patients who had no web after gastrectomy. It would seem that these findings could be interpreted in two ways:

- 1) Gastric impairment appears to be a necessary precondition of nutritional deficiency leading to the development of webs: this is the view of Jacobs, Kilpatrick and Elwood, quoted above.
- 2) Only those patients with significant nutritional deficiencies appeared to develop webs, despite the fact that the majority of the sample (all of whom, presumably, were exposed to an increased risk of nutritional deficiency because of their gastrectomies) did not develop webs. This would seem to support the line of Wynder and Bross: that nutritional deficiency, from whatever cause, is the prime factor in the development of webs.

In the UK, Richards (1969) has drawn attention to the high prevalence of post-cricoid carcinoma in Wales - double the mortality rate of the highest areas in England.

2.3.6 Iron deficiency anaemia in Scotland

There appear to be no published data on spatial variations in haemoglobin levels within Scotland, or on regional differences in admissions for iron deficiency anaemia. An overall picture of anaemia in Scotland (though without the element of spatial

variation) was presented by Donnelly (1968); although now sixteen years old, this paper relates to data from 1965 and, therefore, to conditions obtaining within the latency period of the cancer cases in this study. The salient points from Donnelly's study are summarised as follows: In 1965 more than 250 beds, or the equivalent of one medium-sized Scottish hospital, were wholly committed to the treatment of patients with some form of anaemia. Anaemia patients took up some 91,500 bed-days per year. Between 1961 and 1965 the number of males discharged from hospital with a primary diagnosis of anaemia increased by 30%, 916 to 1,190; the number of females so discharged increased by 22%, from 1,884 to 2,296. Much of this increase, however, was among the very elderly, so much so that, despite their declining representation in the age groups, they weighted the overall rates. Iron deficiency anaemia (ICD 291) and anaemias 'unspecified' (ICD 193) together accounted for approximately two-thirds of all anaemias. Donnelly cautions the reader that multiple admissions of some individuals may have inflated the discharge rate; he also points out that (in 1968) '...there is no available measure of diagnostic accuracy.'

Other than Donnelly's work there is little else on anaemia in Scotland. Simpson and Gourley (1971) studied the prevalence of anaemia in female factory and mill workers, with the intention of discovering whether or not anaemia, if present, affected work performance. Although of limited interest as far as this study

is concerned, the authors cite other works in which (inter alia) it was found that anaemia was present in '...nearly 50% of women aged 18-55 years from the poorer areas of Aberdeen.' Another study cited by Simpson and Gourley showed that in one general practice, over a five year period, 25-30% of women aged 15-34 presented with iron deficiency anaemia.

In hopes of discovering unpublished data on haemoglobin levels or the incidence of anaemia in south-west Scotland, the author contacted the West of Scotland Cancer Surveillance Unit, and the Western Infirmary Department of Haematology, both in Glasgow: to no avail. Both respondents were unanimous in stating that published studies of anaemia variations did not exist and that the information sought at present existed only on hospital discharge data (which, in any case, are notoriously difficult to link accurately with the Cancer Register (Gillis, personal communication, 1984)). One reply, however, effectively ended hopes of finding overt Plummer-Vinson syndrome in the west of Scotland: a correspondent from the Western Infirmary could not recall having seen one case in twenty years as a practising haematologist (R.M. Rowan, Department of Haematology, Western Infirmary, Glasgow, personal communication, 1984).

2.4.0 Cancer and blood group

It has been reported that individuals with blood group 'A' have a 20% greater risk of developing stomach cancer than those with blood group 'O': this has been observed in both high- and low-risk areas of the world (Doll and Peto, 1981). It seems unlikely, however, that any similar relationship exists between blood group and cancer of the oesophagus. Rose (1984) failed to find any significant correlation between blood group and oesophageal cancer in the endemic area of the Transkei, while Day (1984), in the course of a substantial review paper, makes no mention of the subject.

Lack of positive results from other areas does not entirely exclude the possibility that oesophageal cancer and blood group might be linked in Scotland. However, the author's attempts to investigate a possible connection were discouraged by a negative response from the main source of regional information on blood groups (R.Wilson, Edinburgh and South-East Scotland Regional Blood Transfusion Service, personal communication, 1985).

2.5.0 Dietary surveys: availability and validity of information

2.5.1 Dietary data publicly available in Britain: The National Food Survey

The 'National Food Survey' is properly titled: 'Household Food Consumption and Expenditure (Year): Annual Report of the National Food Survey Committee'. The report is issued annually (two years after the title date) and published by HMSO. The report is known informally as the 'National Food Survey' and will be so described here. The Survey consists, in brief, of a randomly-selected group of families, each agreeing to keep a two-week record of food, drink and tobacco purchases and of food eaten outside the home. The number of families in the sample varies from year to year but generally exceeds 7,000 for the whole of the UK. The survey is designed on a 'rolling' basis, with every two-week period of the year covered by a geographically widespread 26th fraction of the total sample; this is to ensure that seasonal variations in consumption are reflected in the returns. Families are randomly selected by social class, the number in each class sample being proportional to the total class size in the country. In 1974 the whole sample consisted of 7,394 families from selected Parliamentary constituencies. Of the total sample, 792 families were from Scotland; these comprised 2,373 persons (average of 3.0 persons per household), 10.7% of all households and 10.7% of all persons in Scotland. The constituencies chosen in 1974 were Coatbridge and Airdrie, Ayr (Ayrshire and Bute), Glasgow (Kelvingrove) and South Angus (Angus and Kincardine).

The National Food Survey publishes food consumption tables, by item, for each country (England, Wales and Scotland) separately, but no details of regional variations in consumption within each country. In theory it would be possible (given permission) to derive such information from the Survey's unpublished data, as the sampling is organised by social class and selected geographical locations (in this case, constituencies). In practice, because the locations chosen are few (around three Parliamentary constituencies each year in Scotland), and because the sites 'rotate', it is not possible to get consecutive yearly data for any one place. There is the added complication that the boundaries of Parliamentary constituencies do not have to correspond with those of other administrative units, such as those of local government or health authorities, nor are the areas covered by constituencies demarcated according to any set of criteria which would be considered rational by a geographer or epidemiologist. It could be argued that food habits change sufficiently slowly for the time intervals separating each return to the same constituency not to matter, and that in time the correspondence between constituency and any other chosen unit of area could be built up using populations at the ward level, or by population of grid squares (to allow for constituency boundary changes). Small sample size is, however, a deterrent to investing this amount of effort. Each of the three Scottish constituencies selected annually includes only one-third (approximately) of the total number of families in the Scottish sample; when the constituency samples are further subdivided into

four social classes, some of the sampling cells begin to be rather small, especially if long intervals between sampling at that location are an additional factor.

Wilkinson (1976) analyses the main findings of the 1974 National Food Survey in a study which attempts to relate diet to socio-economic variables in mortality. His findings show that from region to region and from income group to income group, individual calorie intake varies much less than the consumption of the various foods which supply the energy intake. People do not simply eat more or less of a particular food, if they eat less of one thing they eat more of another. The main variations in dietary patterns are those related to income. Richer people eat much more fruit, more of almost all vegetables except potatoes, more of most kinds of meat except tinned meat and sausages, etc., more milk, cream, cheese and more fat. Poorer people eat less of all these things, substituting for them bread, potatoes and sugar. In 1974 income group 'D' consumed about 40% less fruit and vegetables per caput, about 25% more cereals and 50% more sugar than income group 'A'.

After controlling for a large number of variables such as expenditure on housing, cars, central heating, television, clothing, etc., Wilkinson (op cit) concludes that dietary factors are the most important socio-economic determinants of mortality rates: he ends with the interesting suggestion that '...a data linkage scheme

matching National Food Survey returns with death certificates might prove illuminating.' This suggestion neatly serves to introduce the notion of retrospective dietary surveys in cancer case-control studies.

2.5.2 Dietary studies in cancer research

Byers et al (1983) point out that case-control studies of nutritional factors in cancer only rarely include validation tests of the dietary survey methods. Where validation methods are used they may be of little value, since they are used to test food surveys taken too recently in the history of the cancer to be of any value. The latency period of many cancers is such that it is probably more important to understand the diet of the individual at the beginning of the disease, than it is to know what is being eaten at the time of clinical presentation of the disease. Indeed, Byers et al believe it is possible that '...dietary factors are only important in the earlier stages of cancer development.' Only if the assumption that diets do not vary much over time is valid, would measurement of the presenting individual's food intake be of value - and this point has been insufficiently validated. The authors quote Acheson and Doll (1964) who attempted to discover the dietary habits of patients with cancer of the stomach by asking them to recall their diet one year previously and for a period 15-20 years prior to that. An effort was made to validate the recall procedure by re-testing the subjects three months later and analysing the repeatability of the responses.

The repeatability of the earlier recall data was not good, and in consequence, Acheson and Doll regarded the distant recall technique as unreliable. Garland (1982), on the other hand, reported a study based on an interview of individuals who had been interviewed twenty years before as part of a cardiovascular disease study; here the recall was good, but coloured to some extent by recent dietary practices.

The Byers et al study was based upon a survey of all patients entering a particular hospital during the period 1957-1965 and who were interviewed at the time on their dietary habits. In 1982 a 'convenience sample' (N=175) of those patients still listed in the local telephone directory was re-contacted and interviewed by telephone. The major finding of the study was that diets as recalled from the distant past were better estimates of originally recorded diet than could be got by extrapolating back from current diets. This suggested to the authors that '...if dietary factors ...are thought to be of importance in epidemiologic research, better estimates of past diet might be made by asking study subjects to recall the diets from the distant past, rather than simply using current dietary intake as a surrogate of past intake.'

2.5.3. Comment

Having dealt at length with some of the known associations of diet with cancer of the oesophagus, it must be admitted that - in the Scottish context - actual food intake may scarcely have any bearing on the disease at all. It is true that vitamin levels have a bearing on the development of cancer, that Scottish intake of all fruits and vegetables (except potatoes) is lower than in England and Wales, and that overall rates of oesophageal cancer in Scotland are about twice those in England and Wales. It is also established that income group 'D' consumes less of almost everything except potatoes, bread and sugar than income group 'A', and that oesophageal cancer is overwhelmingly associated with lower socio-economic groups. On the face of it there are good grounds for considering some aspects of the Scottish diet to be a factor in the disease. However, even among the poorest groups in Scotland, symptoms of frank nutritional deficiency are seldom seen, with the single exception of iron deficiency anaemia in women which, in any case, has more to do with iron loss than with lowered iron intake. Such instances of nutritional deficiency as do occur are more likely to be found in the very elderly and in chronic heavy drinkers. There is an epidemiological association here, in that cancer of the oesophagus typically presents in old age and is strongly associated with alcohol consumption. The influence of alcohol on the development of oesophageal cancer is considered next.

CHAPTER THREE: THE SEARCH FOR AETIOLOGICAL AGENTS: ALCOHOL

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3.1.0 PROPERTIES OF ALCOHOL

3.1.1 Alcohol itself probably not a carcinogen

Although an important human teratogen, producing various defects in the babies of women who drink during pregnancy (Kessel, review 1977), alcohol itself is thought not to be a carcinogen (Ketcham et al, 1963; Kuratsune et al, 1971). However, the primary metabolite of alcohol is acetaldehyde¹, which Ames (1984) describes as a mutagen, teratogen, co-carcinogen and possibly a carcinogen. Studies from many parts of the world have implicated alcohol in the development of oesophageal cancer; the relationship, however, is not at all straightforward. In some countries where alcohol abuse results in serious health problems, oesophageal cancer rates are not especially high; Finland is such an example. In France, which has one of the highest incidences of alcohol-related cirrhosis of the liver in Europe, cancer of the oesophagus is a serious problem only in parts of Brittany and Normandy. However, even in 'drinking' countries where oesophageal cancer rates are low, those who do contract the disease are often, indeed usually, found to be heavy drinkers. In contrast, Moslem countries such as Iran and the Soviet Republics of Kazakhstan and Turkmenistan - in which little or no alcohol is drunk - have the highest rates for this cancer in the world. Clearly, although alcohol facilitates the development of cancer, it is not necessary to the initiation of carcinogenesis. It has been proposed that

1. For a summary of the metabolic pathways of alcohol, see Von Wartburg and Ris, 1977.

alcohol is a 'co-carcinogen', a substance defined as '...anything that furthers the action of a carcinogen producing a malignant tumour...a chemical not in itself a carcinogen.' (Butterworths, 1978). Some of the ways in which alcohol is thought to further oesophageal carcinogenesis are discussed below.

3.1.2 The mechanical model

It has been argued that alcohol facilitates the development of alimentary tract cancers by an essentially physical action, i.e. by 'stripping' away the protective mucous secretions, drying out the epithelial surfaces and damaging the cell structure by disturbing intracellular pressure (Lieber, review, 1982); the damaged epithelium is then rendered more permeable to carcinogens. There is strong clinical evidence for this hypothesis since, as Lowenfels (1979) points out: '...most tumours related to excess alcohol consumption appear where there is direct contact with ingested alcohol.' Moreover, dyskeratosis, a condition associated with drying out of mucous surfaces and also regarded as a precancerous condition, is not uncommon in the mouths of heavy drinkers (Anderson, 1972). However, in the light of what is known about the effects of alcohol on nutritional status - and about the association of nutritional status with cancer - the mechanical model by itself is almost certainly too simple an explanation. In the case of the oesophagus, the simple mechanical model has to take into account the short time that

alcohol remains in contact with the oesophageal mucosa. Toyada (1975), in an experiment to measure the diffusion of unchanged ethanol at different sites along the alimentary tract, found that 7% was absorbed by the mouth, 7% by the pharynx, 2% in the oesophagus, 20% in the stomach and 64% in the ileum. In the normal healthy individual the oesophageal epithelium is unkeratinised, unlike the mouth, where there are many keratinised sites (Grays, 1973). It is reasonable to suppose, therefore, that the brief time taken for liquids to pass through the oesophagus is the main reason for the small proportion of alcohol diffusing at this site.

3.1.3 Contaminants of alcohol

Reports from southern Africa (McGlashan, 1969; Cook, 1971; Reilly, 1976) and from Puerto Rico (Martinez, 1969) have implicated beers and spirits (both grain and sugar based): the emphasis in all cases has been on the home-brewed or illicitly distilled product. The search for potential carcinogens in these beverages has disclosed nitrosamines, toxic metals and a variety of industrial and domestic products, from metal polish (Burrell, 1957) to trace remnants of mineral oils, tars and other substances once stored in the tanks and drums used in distilling. None of the findings, however, allowed a categoric conclusion to be drawn, and most authors still consider oesophageal cancer in these areas to be multifactorial in origin, with soil and dietary deficiencies probably acting to potentiate any carcinogens present. Low intakes of calories,

vitamin A and riboflavin have been commented upon in both southern Africa and Puerto Rico (Cook-Mozaffari, review, 1980).

Congeners (the generic name for a number of primary-distillation by-products), include aldehydes, esters and higher alcohols such as amyl alcohol and furfural (Daiches, 1975). In minute (and permitted) quantities, congeners are responsible for the characteristic tastes of whisky, bourbon and cognac; they are almost absent in vodka (Rothman, review, 1975). Many of the aldehydes and higher alcohols are toxic in larger doses and some are also noted for their irritant effect on tissues (see individual entries in Butterworths, 1978). Commercial manufacturers are able to reduce the levels of congeners in their products, by a process of repeated re-distillation and subsequent ageing, to a point which meets the required characteristics of the drink and the requirements of the law. In home-distilled or illicitly distilled spirits congeners are almost invariably present in far higher concentrations than in commercial products (see, for example, Martinez, 1970). In Britain the sale and consumption of 'raw' spirits is prohibited; Binnie (1975) believes that the effect of this legislation protects against oral and other upper-alimentary tract cancer to an extent greater than generally realised.

In Brittany and Normandy, cider and calvados are produced even today by small-scale enterprises, often by individual farms and with much variation in quality. These beverages have been the subject of an

intensive search for contaminants, in particular N-nitrosodiethylamine and N-nitrosopiperidine (Tuyns, 1982). Although nitrosamines were detected in many samples, Tuyns (op cit) reports that the concentrations were so low that the substances could not reasonably be held responsible for excess oesophageal cancer. However, Tuyns further reports that more recent work by Griciute et al (1981) may provide an explanation of how minute doses of nitrosamines, incapable of producing oesophageal cancers by themselves, have produced an increased incidence of tumours in experimental animals when administered with ethanol.

In a much publicised study (see also section 2.1.2) Walker et al (1979) analysed wines, beers and spirits from many countries; a number of beers and a few brands of Scotch whisky were found to contain appreciable amounts of nitrosodimethylene, a powerful carcinogen in animals (concentrations ranged from 0-2ppm in whiskies and from 0.4-7ppm in beers). Citing Jensen (1979), Tuyns (op cit) states that a well-designed longitudinal study on the mortality experience of Danish brewery workers showed clearly that the increased risks observed for cirrhosis of the liver, accidental deaths and cancers of the oesophagus and larynx were those which could be expected from the alcohol component of beer alone; in other words, the nitrosamine content was, or appeared to be, irrelevant.

3.2.0 Malnutrition in chronic heavy drinkers²

There is an extensive literature on the association of malnutrition with chronic heavy drinking, and a correspondingly large literature on the association of malnutrition with cancer. The alcohol-malnutrition sequence involves a complex process of low income, food substitution, insufficient food, alcohol-depressed appetite and alcohol-related malabsorption and metabolic malfunction. However, just as not all alcoholics develop liver cirrhosis, not all chronic drinkers are malnourished nor, when drinkers do become malnourished, are the manifestations of nutrient deficiency always the same.

Broadly, chronic heavy drinking can lead to a state of malnutrition in two ways: by allowing alcohol to replace fats and carbohydrates in energy metabolism and by interfering with nutrient absorption and metabolism. Alcohol provides fully-usable energy at the rate of 30kJ (7kcal)/g and, for example, a man weighing 70 kg can get 5040kJ (1176kcal) a day from alcohol when oxidising it at a constant rate of 0.1g/kg/hr. This means that alcohol can provide up to half the total daily energy needs of a moderately active person (Pekkanen and Forsander, review, 1977). As alcoholic beverages are poor in essential nutrients (McCance and Widdowson, 1973), it becomes difficult for heavy drinkers to satisfy nutritional needs with normal food unless total energy intake increases. In moderate-to-heavy

2. The terms 'chronic heavy drinker/drinking' are used here in preference to 'alcoholic' or 'alcoholism' - the latter terms are properly used to describe a well-defined syndrome of mental and physical dependence on alcohol, accompanied by behaviour disturbances.

drinkers this does happen, with obesity as the inevitable consequence. In very heavy drinkers, however, the appetite-depressant effect of alcohol (Wallgren and Barry, 1970) means that essential nutrient requirements are not met by other foods.

There are also economic and behavioural aspects to the substitution of alcohol for food. Because heavy drinkers often suffer a decline in job status and also figure disproportionately among the unemployed (there is a tendency for known drinkers to be 'shed' or laid-off first when industries contract (Rix et al, 1982; Plant, 1979)), their reduced circumstances may lead them to purchase less food, or to substitute cheaper, starchier foods which may not supply enough essential nutrients. Finally, the compulsive drinker in reduced circumstances may, given the choice of buying alcohol or food, opt for alcohol.

3.2.1 Protein malnutrition

Many chronic heavy drinkers exhibit symptoms of protein malnourishment (Olsen, 1968), though whether this is because of low protein intake or faulty metabolising of amino acids is a matter of variation between individuals. Abnormally low levels of more than 20 amino acids in the plasma and urine of alcoholics were noted by Rosic et al (1975). It is reasonable to assume that faulty metabolising of amino acids results in generally impaired health, as enzymic and hormonal systems, tissue repair, maintenance and cell

replication are all affected; the latter aspect alone has important implications for oncogenesis. As well as being damaged by the irritant properties of alcohol (as, for example, in gastritis and peptic ulcer), it is well known that the intestinal mucosa may be damaged by protein deficiency (Mezey, 1975). Dietary protein deficiencies may also lead to certain vitamin deficiencies which have been associated with cancer of the oesophagus in several epidemiological studies (discussed below).

3.2.2 Mineral and vitamin deficiencies: general

Mineral deficiencies associated with chronic heavy drinking include those of magnesium, sodium, zinc, calcium and iron (Wallgren and Barry, 1970; Somogyi and Kopp, 1976). Associated vitamin deficiencies include those of thiamin, nicotinic acid, riboflavin, ascorbic acid, folic acid and some other B group vitamins (Olsen, 1968; Sinclair, 1972; Paine et al, 1973; Veitch and Lumeng, 1976; Dastur et al, 1976). As far as vitamin deficiencies are concerned it is again difficult to separate dietary from metabolic factors. For example, vitamin B deficiency in heavy drinkers may be due to lowered intake but there is also evidence that ethanol interferes with the absorption of B group vitamins and, in so doing, produces deficiency symptoms (Sorrel et al, 1975).

3.2.3 Vitamin A deficiency

Animal experiments have shown that vitamin A deficiency, often accompanied by riboflavin deficiency (riboflavin deficiency is seldom seen on its own and is usually manifest as a complication of the pellagra syndrome (Olsen, 1968)), and is associated with carcinoma of the stomach, oesophagus, naso-pharynx and lung; and that administering vitamin A and riboflavin inhibits squamous metaplasia and squamous-cell tumours in these organs (Wynder and Klein, review, 1975; Berg, review, 1975; Basu et al, 1975; Dickerson and Basu, review, 1978). Although these results do not prove a causal relationship, there is some corroborative epidemiological evidence from Norway, where a negative association between levels of dietary vitamin A and cancer of the lung and trachea have been found (Bjelke, 1965). A possible explanation for the observed connection between vitamin A and lung cancer - and one which may equally serve for oesophageal cancer among smokers - is that vitamin A deficiency enhances the binding of benzo(a)pyrene and its metabolites to tracheal-epithelial DNA (Genta et al, 1974): these results, it should be made clear, were obtained in hamsters. Lowenfells (review, 1979) remarks that, '...if the same mechanism were found in humans...one could easily imagine why a heavily drinking, vitamin-deficient individual exposed to a carcinogen (such as contained in tobacco smoke) might have an increased risk of cancer.'

3.2.4 B-group vitamin deficiency

Dastur et al (1976) suggest that dietary protein deficiency (defined as less than 38g/day) may also lead to deficiencies of vitamins such as thiamin, biotin and ascorbate, poor uptake of riboflavin and poor retention of riboflavin in the liver. Nicotinate deficiency can also reduce riboflavin stores and, in turn, lack of riboflavin reduces the biosynthesis of tissue folate and can also lead to pantothenate deficiency. A secondary deficiency of riboflavin may result from its increased excretion. Kmet (1970), citing McLester et al (1952), points out that people on high carbohydrate diets need a vitamin B intake higher than average. People low on the socio-economic scale, or those whose economic status is impaired by heavy drinking, are known to have high carbohydrate diets as they seek to satisfy appetite with bread, biscuits, chips and sugar. Thus, the heavy drinker, while needing more vitamin B than the normal requirement, is liable through poor uptake and malabsorption to receive less. McCoy (1978) suggests that riboflavin deficiency may act to promote oro-pharyngeal cancers in drinkers who smoke, by the following mechanism: Deficiencies of riboflavin and/or iron, together with heavy drinking, inhibits mitochondrial nucleotide transport and results in decreased ATP³ synthesis. The damaged cells then produce increased NADPH,³ which increases the metabolic activity of pro-carcinogens.

3. ATP : adenosine triphosphate

NADPH: accepted abbreviation for the reduced form of nicotinamide adenine dinucleotide phosphate (Butterworths, 1979).

3.2.5 Vitamin C deficiency

Reduced tissue stores of ascorbic acid have been noted in various forms of cancer (Burkitt, 1971); in addition, there is a large literature on the use of ascorbic acid to alleviate symptoms and arrest the progress of some tumours, though the latter aspects are the subject of much contention (Cameron and Pauling, 1973; Hughes, review, 1973; Cameron et al, 1976; Alcantara and Speckman, 1976). Reduced levels of ascorbic acid in cancer patients need not indicate a causal relationship (between lack of vitamin and cancer), since low tissue levels could be caused by the disease itself (Dickerson and Basu, review, 1978). However, vitamin C is involved in so many processes relevant to oncogenesis that low intake must at least be regarded as a possible predisposing factor. Vitamin C helps the absorption of iron from food in the intestine into the bloodstream and its lack in the diet may play a partial role in the development of sideropaenic dysphagia (see section 2.3.4), a known precursor of oesophageal cancer in women. Vitamin C also assists in the formation and repair of connective tissue and a lack of it in the diet, particularly in the case of heavy drinkers, may render the body unable to make the necessary repairs after repeated mechanical or chemical insult; there is both direct and indirect evidence that the vitamin is important in disease - or injury-induced stress (Dickerson and Basu, op cit). Bjelke (1974) has shown a protective effect of vitamin C in gastric cancer, as measured by the intake

of raw fruit and vegetables. However, although the histological structure of the alimentary tract follows the same general pattern throughout its length (Grays, 1973), it is not known whether Bjelke's findings can be extrapolated to the oesophagus.

3.2.6 Prevalence of malnutrition in heavy drinkers; an estimate from US data

While the epidemiological links between alcohol, nutrient deficiencies and cancer are very strong, it is nonetheless important not to exaggerate the incidence of even mild malnutrition among drinkers. Olsen (1968) provides the following note of caution: '...the prevalence of mild malnutrition in alcoholics, detected by biological examination of nutrient stores, probably does not exceed 20%, with frank deficiency disease being less than 3% (US data). This improvement in the nutritional status of alcoholics over the past twenty years is no doubt partially due to the fortification of foods with B-complex vitamins, but is also due to the generally better economic status of populations and the availability of foods. It should be remembered that chronic alcoholics generally are not continuous drinkers: they are intermittent drinkers and, although they eat poorly or not at all when drinking, they may eat adequately during periods of sobriety.'

3.3.0 Indices of alcohol consumption and abuse

Any attempt to explore the risks generated by alcohol abuse, be it the risk of cancer, cirrhosis of the liver, accidental death ... or whatever, encounters the problem of estimating the number of heavy drinkers in the study population. Four principal indicators are in common use: per capita consumption (estimated from sales and excise figures and sample surveys); cirrhosis of the liver; arrests and/or convictions for drunkenness and drunken driving; psychiatric admissions to hospitals for reasons of alcohol psychosis or dependence. None of the above indices is entirely satisfactory. The problems inherent in the use of the indices and, in particular, the degree of confidence with which data on cirrhosis of the liver can be matched with oesophageal cancer are discussed below. Apart from some French, American and Australian references, the majority of the sources reviewed relate to the UK, with the emphasis on sources which shed light on the Scottish situation.

3.3.1 Problems of relating per capita consumption to drinking patterns

The relationship between per capita consumption, drinking patterns and alcohol-related problems is highly controversial and the scale and complexity of the issue puts it beyond the scope of this discussion; the arguments have been exhaustively dealt with by, among others, de Lint and Schmidt (1971), Duffy (1977), Duffy and

Cohen (1978), Cartwright et al (1978) and Plant (1979). It must suffice here to say that theory constructed upon the work of Lederman (1964) holds that alcohol consumption is highly skewed, with the majority of drinkers consuming relatively small amounts of alcohol, and successively smaller fractions of the drinking population consuming increasingly larger amounts. Theory also predicts that, as gross alcohol consumption rises, there will be a redistribution of drinkers into the higher consumption categories, with the bulk of the increased consumption being due to already heavy drinkers drinking more. The findings of Cartwright et al (op cit) broadly confirm this view. Although total consumption of alcohol in the UK increased 47% between 1965 and 1974, the authors found that the proportion of abstainers in the population remained nearly constant and that the increase in per capita consumption was not due to more frequent light drinking but to increased consumption among already heavy drinkers. Dight (1970) in a sample of self-reporting Scottish drinkers, found that 30% of the total alcohol reportedly consumed by the group had been drunk by only 3% of the drinkers. Cartwright et al (op cit) noted that the rise in alcohol consumption during the period 1965-74 was also accompanied by a rise in alcohol-related crime and hospital admissions for alcoholism and alcohol-related disease.

3.3.2 Alcohol surveys: general comments

Most information on drinking patterns is derived from surveys which record admissions of what people drink (Plant, 1979). Apart from the notorious untruthfulness of alcoholics and the difficulty of getting accurate information from them (Edwards et al, 1967; Wilkins, 1974), there are also cultural differences in how people regard their drinking: what might be confessed with reluctance in the Home Counties could well be the subject of boasting in Glasgow; distortions occur at both ends of the spectrum. Plant (op cit) makes the following general criticisms of alcohol consumption surveys: Most surveys have been chosen by a supposedly random process from electoral registers - but this is a more selective process than at first appears, since important sub-groups such as the homeless, vagrants, or people in long-stay institutions are excluded; most surveys are geographically small, yet it has been shown that there can be large variations in drinking habits in towns as little as 40-50 miles apart (Plant and Pirie, 1979; Cummins et al, 1981). The Family Expenditure Survey, often consulted for information on drinking habits, may not present an entirely accurate picture, in that the two-week diary kept by each respondent is usually filled in by wives, who record their subjective impressions of their husband's alcohol consumption. Many authors (e.g. Popham, 1972; Schmidt, 1972; Pernanen, 1974), noting the discrepancies between admitted consumption figures and alcohol-related harm in the study

populations, have stressed the near-universal problem of under-reporting (between 20 and 70%, depending on the country, according to Pernanen (op cit)). Finally, morbidity studies which include drinking histories of persons suffering from alcohol-related disease or trauma, or which deal with the prevalence of health problems in groups of heavy drinkers, rarely include control samples and are, in consequence, unhelpful when it comes to calculating risk factors in the general population (Bruun et al, 1975).

3.3.3 Alcohol consumption data available in the UK

The research studies reviewed in these pages, together with the Family Expenditure Survey and National Food Survey (reviewed in section 2.5.1), provide the main sources of publicly available information on alcohol consumption levels in the UK. Additional sources are available on a commercial basis, of which the two largest are the National Drink Survey run by Nestlé and Company Limited, and the Family Food Panel, run by Taylor Nelson Associates. These two surveys differ greatly in scope and methodology and, in their turn, are different from the National Food Survey.

The National Drink Survey: Nestlé and Company Limited. The Nestlé survey monitors consumption of all types of beverage, not just alcohol. The survey operates throughout the UK on a continuous sampling basis; in any one year about 11,000 people will be

interviewed, of whom some 10% will be from Scotland (in 1983 there were 1,025 Scottish respondents). Interviewers ask respondents about their consumption of beverages on the previous day: type of beverage, brand name if known, number of cups, glasses, pints, etc. Alcohol consumption is converted into standard units (q.v.). Respondents are also asked when and where each beverage was drunk, the survey thus recording the self-reported consumption of individuals both in the home and outside (in contrast to the two official surveys, where one member of the family records his or her impression of consumption by other members of the family). In Scotland the sample is drawn only from the Central Lowland region; there is no breakdown of consumption levels within the sample, as for example between Glasgow and Edinburgh.

The Family Food Panel: Taylor Nelson and Associates. The Family Food Panel survey is based on a sample of 2,110 households, of which 200 are in Scotland. Except for a small proportion of people entering or leaving the survey each year, the sample is static; unlike the continuous random sampling of the Nestlé survey or the rolling sample technique employed in the National Food Survey, the Family Food Panel enlists the help of the same respondents year after year. Respondents - generally housewives - record in-home consumption of more than eighty specified foods and drinks, including alcohol. They also provide information on meal patterns and methods of food preparation. Records are kept for two two-week periods and

submitted once every six months. Unlike the National Food Survey and the Family Expenditure Survey, the Family Food Panel does not concern itself with estimating amounts of food and drink consumed outside the home, a fact which limits its usefulness to the alcohol epidemiologist. However, given that limitation, the detailed reporting and long-term relationship built up with respondents suggests a high degree of confidence may be placed in the survey results. The static sample also means that longitudinal profiles of individual consumption can be built up, a facility not present in the National Food Survey. Unfortunately, the Family Food Panel treats all Scotland as one region, and, although data could be analysed to produce information on spatial patterns, this is not done.

3.3.4 Cirrhosis of the liver as an indicator of heavy drinking prevalence

Not all cirrhosis is due to alcohol abuse: other conditions which can lead to cirrhosis are poor nutrition (a deficiency of choline has been shown to cause liver cells to accumulate fat; these cells subsequently become necrotic, being replaced by fibrous tissue), repeated acute hepatitis (or even chronic mild hepatitis) and extra-hepatic obstruction (gallstones and carcinoma of the head of the pancreas can both lead, via jaundice, to biliary cirrhosis) (Lieber, 1982). In the alcohol literature, therefore, a distinction is usually made between other forms of cirrhosis and alcoholic cirrhosis ('cirrhosis with mention of alcohol', ICD 571.0). In the years

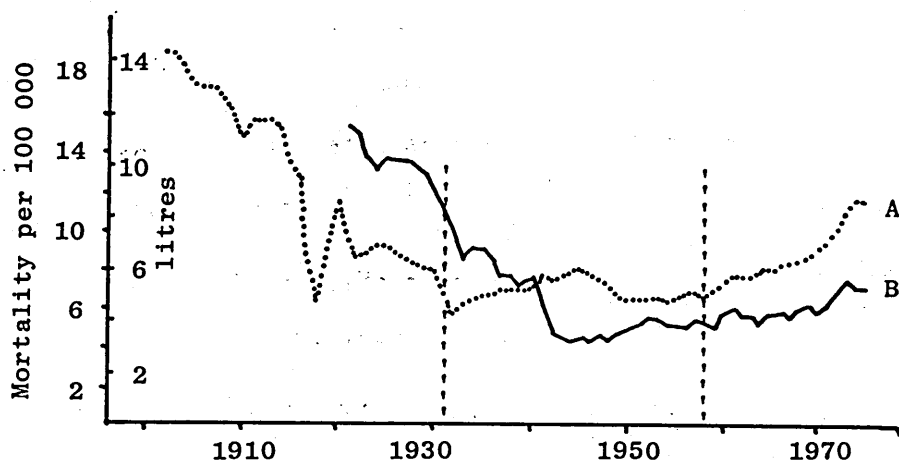
1969-73, deaths reported as due to alcoholic cirrhosis in the UK accounted for 15% of male and 8% of female deaths from all cirrhoses, according to Donnan and Haskey (1977). Higher figures, however, have been reported from regional studies: a recent survey in south London showed alcoholic cirrhosis accounting for 65% of total cirrhosis (cited in Royal College of Psychiatrists, 1979); Plant (1979) believes the figure may be nearer 70%.

Until recently, cirrhosis⁴ was generally accepted as a useful indicator of heavy drinking (Schmidt, 1977; Williams and Davies, 1977; Royal College of Psychiatrists, 1979) and anyone investigating the incidence of a known alcohol-related condition such as cancer of the oesophagus would naturally examine cirrhosis levels for clues to the number of heavy drinkers in the study population. However, the relationship between cirrhosis and alcohol now appears less straightforward and the value of cirrhosis rates as an indicator of drinking prevalence has been called into question (Plant, 1979; Skog, 1980). Moreover, although there are good correlations, both temporal and spatial, between alcohol consumption and cancer of the oesophagus, there is a less consistent relationship between cirrhosis and oesophageal cancer.

According to Walgren and Barry (1970): 'French dietetic studies

4. Henceforth in this work, 'cirrhosis' should be taken to mean 'alcoholic cirrhosis of the liver', unless otherwise qualified.

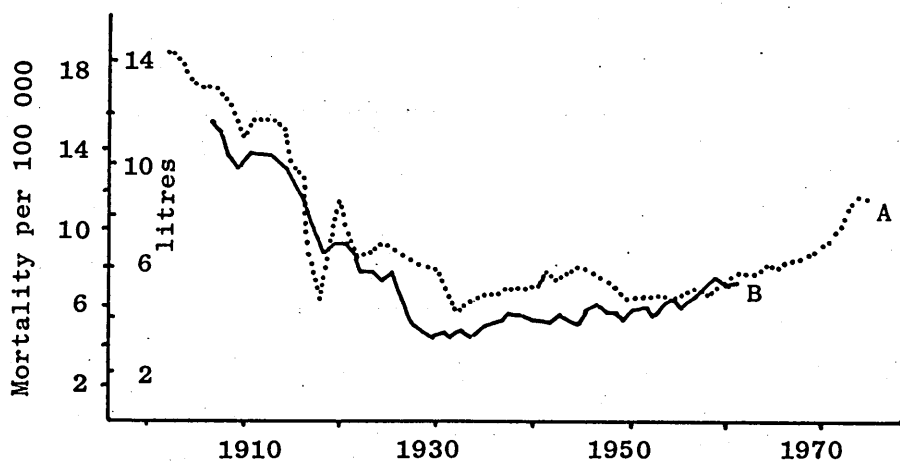
FIGURE 2: TIME TRENDS IN ALCOHOL CONSUMPTION AND LIVER CIRRHOSIS



Liver cirrhosis mortality in males aged 30 years and over in England and Wales, 1921-1975 (curve 'B'), and per capita consumption of alcohol in the population of Great Britain, aged 15 years and over, 1902-1975 (curve 'A'). The vertical broken lines indicate the period 1931-1958, referred to in the text.

Source: Skog (1980).

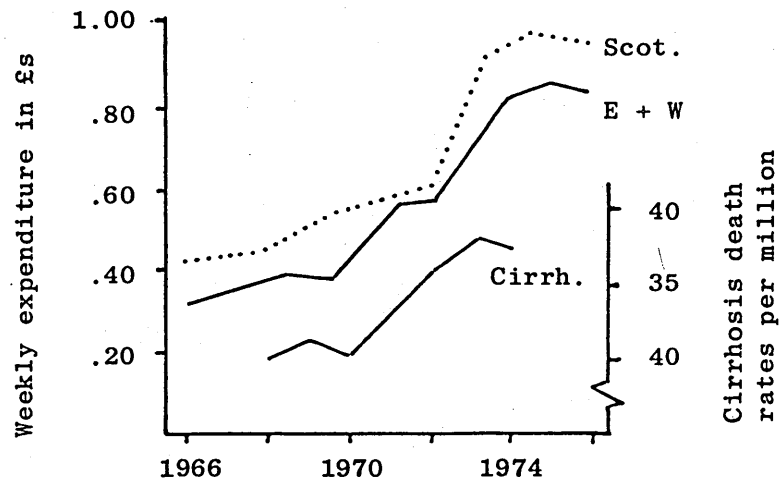
FIGURE 2a: Curve 'B' (see above) 'time-shifted' back 15 years: details in text opposite.



show a clear relationship between severe cirrhosis and a large proportion of calories derived from alcohol. Approximately 160g alcohol (averaged out at 2.5g/kg bodyweight) daily seems to constitute an upper limit that cannot be exceeded without grave danger of hepatic lesion.' Pequignot (1974) puts the damage threshold very much lower and regards a daily intake of 40-60g as potentially cirrhogenic.

A recurrent problem for alcohol epidemiologists is that in spite of the clear links between cirrhosis and heavy drinking, not all heavy drinkers develop cirrhosis (this applies to other alcohol-related diseases). Wilson (1980) writes: '...only a small proportion of alcoholics die of cirrhosis...nevertheless, it has been shown that over long periods changes in the death rate for cirrhosis of the liver were associated with similar changes in other indices of alcohol abuse.' Skog (1980) agrees that the correlation shows up well over time, but argues that cirrhosis is of limited use as an indicator of current heavy drinking because of the time lag involved. As a case in point, Skog (op cit) cites the large negative correlation ($r = -.68$) between alcohol consumption and cirrhosis mortality observed in England and Wales between 1931 and 1958 (Figure 2). However, if a longer period (1921-1975) is taken, the correlation ceases to be negative and becomes weakly positive. By introducing a corrective 'lag factor', and by adjusting its value to achieve optimum fit, Skog is able to show that consumption and cirrhosis trends correlate very well indeed ($r = .87$). Skog stops short of performing the simple exercise of superimposing the time-shifted cirrhosis curve over the consumption series. When the cirrhosis curve is moved left, there comes a point at which the two series match extremely well (Figure 2a): in particular, two sharp dips in

Figure 3: Trends in expenditure on alcohol in England, Wales and Scotland (1966-76) and cirrhosis death rates in England and Wales (1968-74).



Sources: Adapted from data in Haskey et al (1983) and Royal College of Psychiatrists (1979)

alcohol consumption (one around 1908-10, the other during the 1914-1918 War) are obviously replicated in the superimposed cirrhosis curve.* The shift at this point is equivalent to a time lag of some 15 years. Any residual asymmetry between the series is, in Skog's view, caused by instability in the time lag (probably because the lag tends to be larger when consumption increases than when it decreases: which in turn may relate to differences between disease development and remission times (referred to again on page 113)). Schmidt (1978) believes that whatever the reasons for the 1931-58 divergence between consumption levels and cirrhosis rates there are now 'unmistakeable signs' that the situation in Britain is coming into line with that in other countries. If appearances are to be believed, the time lag in the United Kingdom virtually disappeared between 1968 and 1974: a 27% increase in cirrhosis mortality was matched by a similar rise in expenditure on alcohol (Figure 3). However, the cirrhosis rates may have been responding to a previous rise in alcohol consumption. Skog (op cit) cautions against accepting a high correlation as evidence of a good relationship, saying that spurious covariation in time series is a well known problem for which safe control methods are not available.

* This observation raises some difficult questions: e.g. What mechanism can possibly link a transient rise or fall in alcohol consumption with a corresponding rise or fall in cirrhosis mortality several years later? Chilvers et al (1979) surmised that drinking habits founded between ages 20 and 30 were a factor in the subsequent development of oesophageal cancer: it may be that a similar mechanism is at work in the case of cirrhosis. If this were so, however, we should expect the process to become apparent through a cohort effect, rather than be seen across the age groups, as seems to be shown by Skog's cirrhosis curve. Skog himself does not attempt an explanation but merely remarks that 'extensive theoretical analysis' is still required.

Plant (1979), commenting on the inadequacies of cirrhosis as an index of heavy alcohol consumption, points out that not only does the relationship vary over time, there are also marked variations from one country to another. Killich and Plant (1981) looked at the intercorrelations of three causes of mortality (cirrhosis, accidental poisoning and suicide) with alcoholism and alcoholic psychosis, and found substantial differences in patterns of correlation in comparing Scotland with England and Wales. (The work of Killich and Plant is reviewed in more detail in section 3.5.4.). Davies (1979) also noted the puzzling variations, both spatial and temporal, in UK cirrhosis mortality rates (see below).

TABLE Death rates per 100,000 population from
 cirrhosis in the United Kingdom: 1964-74

	1964	1974	% change
Scotland	4.8	6.3	+31
Northern Ireland	2.7	4.3	+59
England & Wales	3.0	3.8	+27

Source: Davies (1979)

Davies (op cit), commenting on the consistently higher cirrhosis death rates in Scotland, writes: 'Given that the per capita consumption of pure alcohol is about the same (or slightly higher) in Scotland than in England and Wales, the elevated rate of deaths from cirrhosis of the liver in Scotland is hard to explain purely in terms of per capita alcohol consumption.'

Finally, an inbuilt distortion is created by the use of cirrhosis mortality data. Macrae (1972) writes: 'Little can be deduced from [cirrhosis mortality], for cirrhosis is not necessarily a consequence of alcoholism, and when it is would typically be a remote one, i.e. not causing death until many years after onset of the initial illness.' Plant (1979) puts the matter more briefly: '...cirrhosis mortality tells us only how many dead alcoholics there are, not how many living ones.' Differences in the dose-response and latency periods as possible explanations of the ill-fit between cirrhosis and oesophageal cancer mortality are discussed in section 3.3.6 below.

3.3.5 Cirrhosis and occupation

There are very large differences in occupational mortality from cirrhosis; among occupations with the highest risk Plant (1979) lists the following:

Standardised Mortality Ratios for cirrhosis
in men aged 15-64, by occupation, data for
the years 1970-72.

	England & Wales SMR
Publicans/innkeepers	1576
Deckhands, ships' pilots, engineers	781
Barmen/barmaids	633
Fishermen	595

Source: Plant (1979).

Other occupations with high SMRs were lorry drivers, train drivers, shunters, rail pointsmen, cooks, doctors and winders and reelers in the textile industry.

Alcohol consumption in the above occupations is ascribed first of all to access: barmen, hoteliers, etc., have it to hand all the time, doctors 'need' it because of stress and can afford it because of high incomes. Second, some industries attract heavy drinkers: occupations such as fishing or the merchant fleet, which involve loneliness and danger, have traditionally attracted misfits who may be heavy drinkers before entering the occupation. Once there, the availability of alcohol and relaxed attitudes to its use exacerbate the problem. In some industries, for example brewing and distilling, this 'drift' factor has long been a notable feature (Plant, 1979, quoting Wilson, 1940).

Studies from the USA (Cahalan and Kissin, 1966; Cahalan and Room, 1972) and from the UK (London: Edwards et al, 1972; Scotland: Dight, 1976; Plant and Pirie, 1979) have shown a 'U' shaped distribution of alcohol problems, with males in both the lowest and highest status occupations tending to be the heaviest drinkers. In Scotland the picture is complicated by the fact that non-manual workers are more likely to be regular and moderate drinkers than are manual workers; manual workers are likely to be either abstainers or heavy drinkers (Plant and Pirie, 1979). Low-risk occupations

in England and Wales include agricultural workers, teachers, carpenters and joiners, machine tool setters, fitters and machine erectors. The pattern of low-risk occupations in England and Wales is certainly not reflected in Scottish figures (see Chapter 6).

3.3.6 Cirrhosis and oesophageal cancer: general

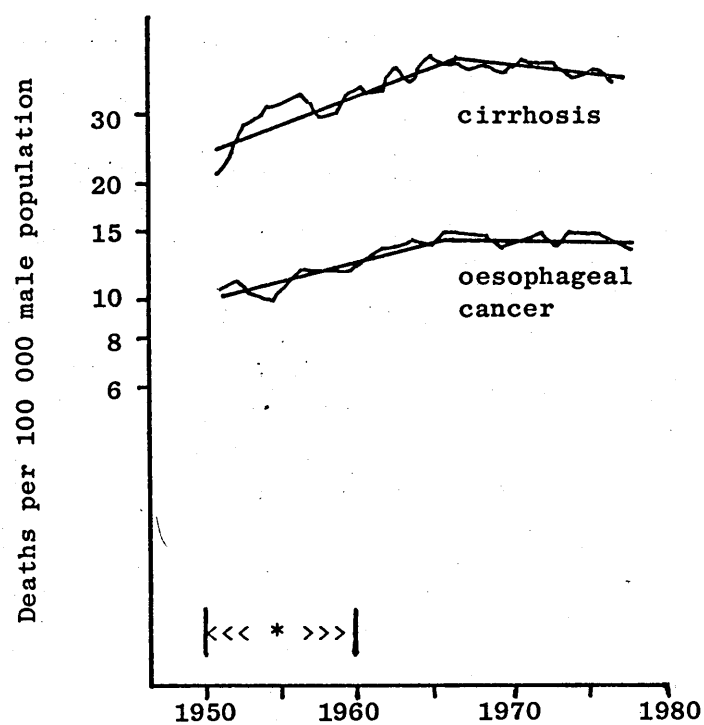
Keller (1967) matched two groups of heavy drinkers by amount and duration of drinking ('duration' here means the time elapsed from onset of heavy drinking behaviour); one group had head and neck cancers, the other group contained non-cancer controls. 22% of cancer patients had cirrhosis, compared with 11% of controls. Keller concluded that cirrhosis might actually play a part in the pathogenesis of upper alimentary tract cancer, as distinct from being just another associated product of heavy drinking. Since, among other things, the liver is the central organ of metabolism of protein, carbohydrate and fat, stores vitamins and is also the chief organ of detoxification, a link between liver damage and squamous-cell carcinomas is highly plausible. However, the link between cirrhosis and cancers of the head and neck appears stronger for some sites than for others: Kissin and Kaley (1974) citing Keller (1967) and Tuyns (1970), state that cancers of the mouth and pharynx co-exist more often with cirrhosis than does cancer of the oesophagus at any given level of alcohol consumption.

FIGURE 4

Mortality from cirrhosis and oesophageal cancer in France.

Time trends 1951-1975

Males



<<*>> Period of active anti-alcohol legislation

Sources: Audigier & Tuyns (1981)
Bernard (1980)

In a more recent paper Tuyns (1982) reports on the close correspondence between cirrhosis and cancer of the oesophagus in France.⁵

(The background to the trends reported by Tuyns are as follows:

alcohol consumption in France in the period 1954-55 was 30.4 litres per caput (measured as pure ethanol), the highest in the world (Lereboullet and Biraben, 1964). As a result of stringent measures by the government in the 1950s (reviewed in Bernard, 1980) consumption fell markedly, until by 1975 it had reached 16.90 litres per caput (Produktschap voor Gedistilleerde Dranken, 1975), though it remained the highest per capita consumption in the world.) Tuyns (op cit) reports that oesophageal cancer mortality rates began to level off in 1966 and that cirrhosis mortality stopped increasing at about the same time (see Fig. 4 , facing page).

Unfortunately, alcohol consumption data do not accompany the mortality data in Tuyns' paper. However, one observation prompted by the graph and knowledge of the 1950s government measures is that the increase in mortality from both causes levelled off about ten years after the fall in alcohol consumption. Although ten years is well short of the latency period of either cirrhosis or oesophageal

5. In a very recent paper, Day (1984) describes the variations in oesophageal cancer mortality seen in the French départements as: '...unrelated to mortality rates due to alcoholism': this judgement, however, was based upon a reading of Tuyns (1970). Later works by Tuyns (see above) and by Pequignot (1977) suggest that there is a much stronger relationship between all indices of alcohol consumption and oesophageal cancer in France than at first appeared (see following pages).

cancer, this fact need not cause problems. The time taken for a disease to become manifest is not necessarily the same as that required for its remission when exposure to a causal agent is removed or reduced. There are, in any case, other pointers to the involvement of alcohol. Tuyns also draws attention to the very evident cohort effect seen in French data. Males born between 1902 and 1916 experienced no increase in mortality from cirrhosis of the liver and cancers of the oesophagus and larynx; no similar effect, however, was noted for cancer of the lung. Tuyns says this could be interpreted as being due to the short supply of alcohol during World War II, that prevented those who were young adults at the time from acquiring damaging personal drinking habits. Not only do French data on cirrhosis and oesophageal cancer mortality match gross consumption figures for alcohol very closely, there is an excellent correspondence at the individual level. In the Ille-et-Villaine study (Pequignot, 1977) a sample of the general population over 24 years old and all patients admitted to hospital for cirrhosis, delirium tremens and cancer of the oesophagus were questioned about their daily alcohol consumption. The study produced a clear dose-response relationship to risk for each of the three conditions. The threshold of damage for each condition varied considerably, as did the age of disease onset. Pequignot (op cit) remarks: 'One is led to suggest a comparative natural history of the three diseases considered. The most heavy drinkers (more than 80 g alcohol per day) have delirium tremens at about 45 years of age: those who

consume 20 g alcohol less do not get delirium tremens but may contract cirrhosis of the liver ten years later. Drinkers consuming another 20 g less on average may escape these two diseases and develop cancer of the oesophagus about five years later, usually on the condition that they are heavy smokers. Indeed, the risk is related to the combination of alcohol consumption and smoking for this last disease, since at a constant dose of alcohol the risk increases with the amount smoked and vice versa.'

Australian data also show some cohort effect remarkably similar to that of France and a close correspondence between cirrhosis mortality and cancers of the larynx, oropharynx and oesophagus (McMichael and Hetzel, 1978); a latency period of about thirty years for cancer of the oesophagus becomes evident when mortality data for this cancer are compared with per capita alcohol consumption. Hetzel (1978) states that, although upper alimentary tract cancers are partly related to tobacco consumption, the time trends are quite different to those of lung cancer.

Not all countries, however, produce correlations between cirrhosis and oesophageal cancer as clear as those from France and Australia. Commenting on correlation coefficients from several countries, Bruun et al (1975) note that although there are indications of the expected relationship between cirrhosis and oesophageal cancer, the overall picture is by no means clear. The authors quote the view

of Schoenberg (1971), that the discrepancies - where they exist - arise from a failure common in such correlation data, namely that of not allowing for the different latency periods between exposure to alcohol and development of the disease.

Skog's comments on interpretations of alcohol consumption and cirrhosis mortality trends in Britain have already been noted (section 3.3.4). It would not be true, however, to say that the matter of disease latency has been entirely ignored by British authors; many have taken the subject into account, yet there remains a confusing picture. Binnie (1975), writing of oral cancers, observes: 'Like pipe smoking, spirit consumption shows a downward trend since the turn of the century until the end of the 1940s. Since that time alcoholism seems again to have increased sharply, especially among women (emphasis added). This is indicated both by the statistics for cirrhosis, admissions to special units for alcoholic mental disorders and other statistics for alcoholism. Cirrhosis is a late result of alcoholism and it might be expected that this increase, starting over twenty years ago, might be reflected in the statistics for oral cancer. This has not been the case, and though in France an exceptionally high mortality from oral cancer is associated with an exceptionally high incidence of cirrhosis of the liver, the association between these diseases in England and Wales does not appear to be so close.' Binnie's remarks could also be applied to cancer of the oesophagus.

3.3.7 Cirrhosis: spatial correlation with oesophageal cancer in England and Wales

Chilvers et al (1979) divided the nine pre-1974 standard regions of England and Wales into conurbations, urban areas excluding the conurbations and rural areas, 26 subdivisions in all. Using data for the years 1969-73, SMRs for cirrhosis and cancer of the oesophagus were plotted against each other for each of the 26 areas. Male mortality from these causes was found to be highly correlated on a regional basis ($r = .66$, $p < .01$); for females no such correlation was found ($r = .11$, $p > .1$). The authors believe the low correlation between cirrhosis and oesophageal cancer in women may be due to substantial under-reporting; only 8% of all female cirrhotic deaths are recorded as being due to alcoholic cirrhosis and this is almost certainly a considerable under-estimate. (Under-reporting may not be the sole cause of the discrepancy, however. The cohort effect for cancer of the oesophagus in England and Wales - so clearly seen for men - is much less distinct in the case of women, this despite the steep post-war rise in alcohol-related problems among women emphasised in the earlier quotation from Binnie (1975). It may be that in England and Wales some as yet unidentified agent(s) afford(s) a measure of protection to women against alcohol damage.)

3.3.8 Cirrhosis, oesophageal cancer and beverage type

Earlier cancer correlation studies from France used a composite index of alcohol-related harm consisting of mortality from acute and chronic alcoholism and cirrhosis (Flamant et al, 1964; Schwartz et al, 1966; Lasserre et al, 1967); this gave high positive correlations against mortality from oesophageal cancer ($r = .70$ in Lasserre, op cit). However, when some of the data (Lasserre's) were later re-analysed and alcoholism and cirrhosis were separated, the association of alcoholism to oesophageal cancer was found to be stronger than that between cirrhosis and oesophageal cancer (Tuyns, 1982 - citing a thesis by Lasserre, 1963); revised correlation coefficients not given). Tuyns wondered whether the difference in association indicated that the type of beverage might be important.

In the United States Breslow and Enstrom (1974) found a high correlation for spirits and oesophageal cancer ($r = .68$ in men), beer consumption was more highly correlated with cancer of the rectum ($r = .78$ in men) than with cancer of the oesophagus. In Australia the high mortality rates of people born around 1870-80 were associated with an historic peak in consumption of spirits around 1900-10; the more recent upturn in Australian oesophageal cancer mortality is associated less with spirits than with the threefold increase in beer consumption since World War II (McMichael and Hetzel, 1978). [In passing: The mortality experience of Australians born around 1870-80 is almost exactly

paralleled by that of the corresponding generation in England and Wales. Chilvers et al (1979) found that cohort mortality was strongly correlated with per caput consumption when each cohort was around 25-30 years old: they concluded that drinking patterns established in the individual's early 20s affect alcohol consumption in later life. By inference, these early-formed drinking habits also affect cohort mortality from oesophageal cancer.] In England and Wales, Chilvers et al (op cit) found oesophageal cancer highly correlated with both beer and spirit consumption in both sexes.

TABLE Oesophageal cancer and beverage type
Correlation coefficients - England & Wales

	Beer	Wines	Spirits	Total
Males	0.76	-0.13	0.84	0.82
Females	0.81	0.06	0.96	0.91

Source: Chilvers et al (1979)

The authors conclude that, since mortality is correlated with total alcohol consumption, rather than with any particular beverage, carcinogenesis is probably a product of alcohol alone, rather than any specific ingredient or contaminant of specific alcohol beverages. Given the slender evidence for any role played by alcohol contaminants (discussed earlier) this assessment is probably correct. However, it is at least arguable that their greater power to 'dry out' and otherwise damage the oesophageal mucosa makes spirits more of a hazard than other beverages, and may be responsible for

the slightly higher correlation coefficients recorded.

3.4.0 Scottish alcohol consumption: general remarks

'The French drink steadily and kill themselves with cirrhosis: the Scots drink in bouts and kill their neighbours.' Bill Saunders, Alcohol Study Centre, Paisley (The Observer, 31 March 1985).

In Britain there are accurate figures for commercially produced alcohol and for imports and exports of alcoholic beverages. Useful estimates of home-made beers and wines, etc., can be derived from data on sales of raw materials and equipment. Home distilling is illegal without a licence and the extent of alcohol production in this area is unknown. However, although there are reasonably good figures for alcohol 'moving into consumption', who consumes it, where and how often are matters about which there is much less information. Unfortunately, without some knowledge of consumption at the individual level, or at least some insight into the drinking habits of certain high-risk groups, inferences drawn from per caput consumption data are at best superficial and, at worst, can be seriously misleading. For example: Two individuals may drink the same amount of alcohol in the course of a week, but if one drinks a little each day and the other consumes the entire quantity on Friday night, it is more likely to be the latter who is involved in an accident or is arrested. Nations may behave in similar fashion: there is evidence that Scots drink less often than drinkers in England and Wales, but that in comparison they drink much more on each occasion (Wilson, 1980).

If the relationship of drinking patterns to accidents or arrests for drunkenness is fairly straightforward, the connection with bodily health is much less clear. Is the person who 'binge drinks' more - or less - likely to develop cirrhosis or cancer than the one who drinks the same amount over several days? Bruun et al (1975), citing Leibach (1974), believe the pattern of drinking is irrelevant except insofar as it affects the total amount consumed; the crucial variables appear to be the duration of drinking and the amount drunk. Saunders et al (1984) take another view; they believe that 'resting' the liver by abstaining from alcohol for two days each week reduces the risk of serious liver damage. If this is so, then the Scottish drinking pattern described by Wilson (op cit) should result in more accidents and drunkenness but less cirrhosis. In fact, Scottish indices for drunkenness are, as expected, much higher than those for England and Wales, but so also are indices for cirrhosis (see section 3.5.6).

In later sections reference will be made to amounts of alcohol drunk by various population groups; how do these amounts relate to what is known about 'safe' drinking levels? The Royal College of Psychiatrists (1979), while acknowledging the difficulties in defining safe drinking levels with precision (because of differences in body size, metabolic rate, proportion of lean to fat tissue, etc.), offers the following guidelines: Assuming a degree of under-reporting by heavy drinkers it is reasonable to treat fifty

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7. A recent survey among alcohol researchers (Anderson et al, 1984) found no consensus on the upper safe limits for alcohol consumption. The majority of those questioned believed that alcohol-related damage begins at much lower thresholds than those suggested in the Royal College of Psychiatrists report (op cit): more than 50% of the respondents gave estimates of safe limits which fell below 35 units per week for men and 21 units per week for women. If these lower safe limits do indeed reflect thresholds at which damage occurs, then the numbers at risk must be considerably greater than those given in Wilson (op cit).

units⁶ a week as being the safe limit for men and 35 units a week as the safe limit for women. This translates into the equivalent of four pints of beer a day as the upper limit for men, three pints for women. Wilson (1980), says of the RCP recommendations: '...if these limits are adopted [then] surveys suggest that six per cent of men in England, Wales and Scotland...are drinking an amount which involves a risk of seriously damaging their health in the long term. A much lower proportion of women (one per cent or less in each country)...were exceeding the safe limits.'⁷

3.4.2 Scottish alcohol consumption

Customs and Excise taxation figures are available only for the UK as a whole and so it is not possible to give a total consumption figure for Scotland. Information on consumption within Scotland is scarce and contained within a mere handful of sample surveys (the largest of which (Dight, 1976) had less than 2500 respondents, the smallest (Crawford et al, 1984) had only 190 Scottish respondents). Together with the National Food Survey and the General Household Survey these studies present a confusing and, in some cases, conflicting picture of alcohol consumption and related harm. Dight (1976) found the highest consumption levels in Glasgow and the Clydeside conurbation, the lowest in Aberdeen. Plant and Pirie (1979) found the reverse, with highest consumption levels in the north of Scotland. Data from the General Household Survey (1980) and in

6. A unit is defined as equivalent to one half pint of beer, a glass of wine (4fl.oz/155ml), a small glass of fortified wine (2fl.oz/55ml) of 1/6, 1/5 or 1/4 of an English, Scottish or Irish gill respectively.

7. See footnote on opposite page.

Cummins et al (1981) lent further support to the notion of a north-south decreasing gradient in consumption. However, recent surveys had led Plant (working with others) to abandon the view that there is a north-south gradient in either consumption or alcohol-related morbidity (Crawford et al, 1984). Even in comparatively straightforward matters, such as estimates of average consumption, there are wide variations:

TABLE Per capita alcohol consumption in Scotland, standard units per week, results of 2 surveys			
	Plant & Pirie (1979)	Dight (1976)	% disagreement
Males	12.6*	20.5	47.7
Females	2.9	4.8	49.3

Source: Plant and Pirie (1979)

Lack of consensus among Scottish alcohol epidemiologists and the absence of a definitive official survey, leaves the new researcher with little confidence in the available data, but also little option but to use what is at hand.

Data in Wilson (1980) appear to show that average consumption in Scotland is almost identical to that in England and Wales:

* Respondents in the Plant and Pirie survey were questioned about their consumption while the Scottish Health Education Unit were running a public campaign on alcoholism. The authors acknowledge this fact may have led some people to under-report their consumption.

TABLE Comparison of average weekly alcohol consumption in England and Wales and Scotland; standard units by age and sex.

Age *	M a l e s		F e m a l e s	
	England & Wales	Scotland	England & Wales	Scotland
20-27	26.6	26.2	9.7	7.7
28-37	19.7	24.9	6.4	6.3
38-47	19.5	20.9	7.7	6.2
48-57	20.1	16.1	7.2	6.1
58-67	15.5	13.5	4.4	3.9**
68+	11.7	6.4	5.0 ¹	
all aged 20+	19.6	19.5	7.0	6.2

Source: Wilson (1980)

* Wilson uses unconventional age groups for reasons connected with data availability

** Age groups compressed because of small numbers

Although average consumption figures for each country are very similar there are differences between corresponding age groups. In Scotland men in the 28-37 year age group drank substantially more than their counterparts in England and Wales; in subsequent age groups consumption by Scottish males falls below that of males south of the border. Opinions differ on the immutability of drinking habits. Kendell et al (1983) state that alcohol consumption tends to fall with increasing age, with a sharp, economically-induced reduction after retirement. In a sample of 'regular' drinkers from the Lothian region (Edinburgh and its hinterland) they (Kendell et al) found that consumption appeared to fall by 0.25 units per year for men and 0.1 units per year for women

(the decline in yearly consumption recorded by Wilson was steeper for men (0.32 units for men) but identical for women). Both these surveys sampled all categories of drinkers and the results reflect the longitudinal drinking pattern of the majority, the light to moderate drinkers. There is abundant evidence, however, that heavy drinking habits acquired in early adulthood tend to persist. Several writers already cited have drawn attention to the importance of early-acquired habits for the later development of alcohol-related disease. Even if the 28-37 year old Scots cohort in Wilson's sample do not continue drinking at the same level, the process of harm consequent on heavy drinking will already have begun. That many of them do continue drinking heavily is borne out by the admissions figures for cirrhosis, the peak period for which is around 45 years (Macrae et al, 1972). [In passing, the latency period for development of cirrhosis in Scotland corresponds closely to that proposed by Pequignot (1977) on the basis of French data (discussed earlier in section 3.3.6.)] Duration of drinking has been mentioned earlier as one of the two main factors connected with the development of alcoholism, cirrhosis and upper alimentary tract cancer; in this respect the divergence in drinking behaviour among young males north and south of the border may go a long way to explain why alcohol-related morbidity and mortality in Scotland is so much higher than in England and Wales. [Although objectively worse, Scottish figures for alcoholism and related harm may appear even worse in comparison with those of England and Wales because

TABLE 10

PROPORTION OF DRINKERS TO NON-DRINKERS IN THE SCOTTISH POPULATION: RESULTS FROM THREE STUDIES

Dight (1976)	M	F	Wilson (1980)	M	F	Crawford et al (1984)	M	F	M	F
	%			%			%		%	
regular	74	22				regular	64.1	38.7	73.7	49.8
occasional	22	42	drinkers	77.8	54.7	occasional	30.3	46.7	24.3	42.6
abstainer	5	12	non-drinkers	22.2	22.3	abstainer	5.6	14.6	2.0	7.5
							Highlands	Tayside		

of differences in classifying and recording events, and in provision of hospital beds, etc. These differences are discussed below in section 3.5.2.]

In one respect there is fairly close agreement between the various Scottish studies; even allowing for regional variations and for some lack of uniformity in presentation of results, it is obvious that drinking is much more prevalent among men than women. Of the total drinking population of Scotland, the proportion of heavy drinkers (those drinking twenty or more units per week) appears to vary considerably from region to region. In the four urban areas investigated by Plant and Pirie (op cit) the proportion of heavy drinkers ranged from 7.6% in Ayr to 15.1% in Glasgow; the differences, however, are not significant. Crawford et al (op cit) found both the highest proportion of drinkers and the highest consumption levels on Tayside; the lowest consumption levels and the highest proportion of abstainers in the Highlands. Although there are too few studies to allow any definitive picture to be drawn,⁷ some of the associations are nonetheless interesting. The Highlands, for example, with the lowest proportion of drinkers and the lowest per capita consumption levels, have one of the lowest SMRs for oesophageal cancer in either sex. Tayside, on the other hand, with both the largest proportion of drinkers and the largest proportion

7. Plant (personal communication, 1984) knew of only three studies dealing with spatial variations in consumption levels.

of heavy drinkers, has - in Dundee - the highest rates for oesophageal cancer. Over the country as a whole, Dight (op cit) found that 30% of all alcohol drunk in a typical week was consumed by only 3% of the total population (5% of all regular drinkers), and that the heavy drinking group consisted almost entirely of men. Plant and Pirie (op cit) found too few female heavy drinkers to warrant statistical comparisons between regions.

3.4.3 Alcohol and social class in Scotland

Males:

Plant and Pirie (1979) found that non-manual workers were more likely to be drinkers than manual workers (88.8% compared with 78.3%), but that those manual workers who did drink were significantly more likely to drink heavily (among drinkers 11.5% of manual workers drank heavily compared with 6.3% of non-manual workers; $p < 0.02$). Wilson (1980) gives no numerical information about the proportions of manual and non-manual workers who drink but remarks that those in non-manual work consistently drank less than those in manual occupations. This accords with the findings of Plant and Pirie cited above, and also with those of Cummins et al (1981). These last authors surveyed smoking and drinking habits in several towns in the UK and found that not only were manual workers consistently more likely to be moderate-to-heavy drinkers and smokers, but also that place of residence exerted an appreciable influence which was independent of class. (The findings of Cummins et al (op cit) are discussed in detail in Chapter Four, section 4.3.1).

Females:

The class picture described above is reversed in the case of Scottish women, among whom drinking prevalence rises with social class, from 28% among those in class V to 74% in class I (Dight, 1976). Not only drinking prevalence: consumption levels among women in social classes I-III were also higher than among women in classes IV-V (Wilson, 1980), though measured intakes were rarely high enough to engender harm (in Dight's survey (op cit) the maximum amount drunk by a man in one week was 189 units, among women it was 44 units).

3.4.4 Beverage preferences

Although their per capita consumption of spirits is twice that of men in England and Wales, beer is still the preferred drink of most Scottish males. Spirits are the preferred drink among Scottish women.

TABLE Beverage preferences (expressed as proportions of average weekly consumption)

	Men aged 20+		Women aged 20+	
	England & Wales	Scotland	England & Wales	Scotland
Beer, lager, cider	75	66	30	15
Spirits	13	28	25	49
Table wine	8	4	18	12
Fortified wine	4	3	28	15
	<hr/> 100	<hr/> 100	<hr/> 100	<hr/> 100

Source: Wilson (1980)

3.5.0 Indices of alcohol-related harm in Scotland

3.5.1 'Global' estimates of alcohol abuse

Donnan and Haskey (1977) produced a range of estimates of the numbers of frank alcoholics in England and Wales; depending on the index used, their estimates were: 155,000 (based on cirrhosis deaths), 235,000 (based on deaths due to alcoholism) and 600,000 (based on deaths due to alcoholism with complications). However, Wilkins (1974), having shown how unreliable doctors can be in diagnosing alcohol problems in their patients and in colluding with patients to minimise or conceal the extent of the problem, concluded that as few as 5% of alcoholics consulting general practitioners were either recognised or so recorded. In the light of what was known or suspected about the extent of under-reporting, Donnan and Haskey (op cit) believed the total number of alcoholics in England and Wales might be as high as 740,000 (1973 figures). Expressed in percentage terms, the estimates in Donnan and Haskey suggested that 0.32%-1.55% of the English and Welsh populations might be alcoholics.

A 1967-69 study confined to the Highlands and Islands area found that 1.11% of males over the age of fifteen were diagnosed as alcoholics, the figure for females was 0.15%, a combined rate of 0.62% (Whittet, 1970). The present author has discovered no exercise relating to Scotland similar to that performed by Donnan and Haskey for England and Wales. Even if such a study did exist,

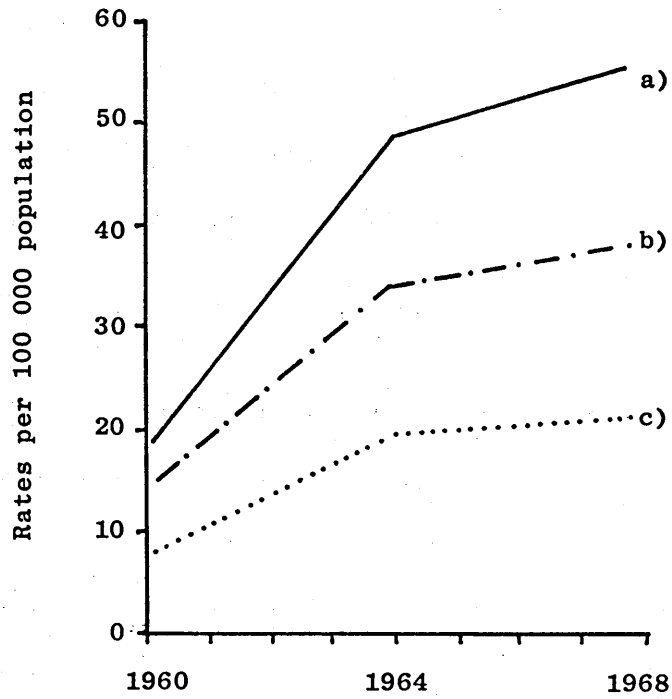
however, it is difficult to believe (*vide* Wilkins, op cit) that much reliance could be placed on the results. Aside from the probability of considerable under-reporting, there are other problems in gauging the numbers of drinkers at risk in Scotland. Scottish drinking habits differ markedly from those in England and Wales - in frequency of drinking and amounts drunk on each occasion, age and social class of drinkers, and in beverage preferences. Moreover, many of the indices commonly used to assess heavy drinking prevalence in England and Wales are suspect in the Scottish context. In the following pages, three such indices are examined in the light of their usefulness - or otherwise - in determining the extent and nature of alcohol abuse in Scotland.

3.5.2 Alcoholism and alcoholic psychosis

The problem, noted earlier, of authors choosing different indices, or of combining several causes to make one composite index, also affects interpretation of the alcoholism/alcoholic psychosis data. In the two main papers reviewed in this section, one set of authors (Macrae et al) select 'alcoholism', the others (Crawford et al) choose 'alcohol dependence, abuse and psychosis'; the two indices are not quite synonymous, although - perforce - they are treated as such here.

Hospital admissions for alcoholism in Scotland showed a steep rise throughout the 1960s, from a total of 18.3 per 100,000 population

Figure 5: Admissions for alcoholism: Scotland



- a) total admissions
- b) first admissions
- c) male first admissions

Source: MacCrae et al (1972)

in 1960, to 56.3 per 100,000 in 1968 (Macrae et al, 1972). After 1968 the overall rate fell, until in 1977 it reached 36.1 per 100,000 (Killich and Plant, 1982). A further reduction seems likely in the wake of the taxation-induced fall in alcohol consumption during the periods 1978-79 and 1981-82 (Kendell et al, 1983). Fig. 5 (see facing page) shows trends in alcoholism admissions during the 1960s.

Macrae et al (op cit) suggest that there are three ways in which the above data might be interpreted. The first is that the data might be taken at face value and the conclusion drawn that the 1960s saw an alarming trend towards earlier onset of alcoholism in Scotland. A second possibility is that increased awareness of alcohol problems among the medical profession and general public alike, led people with drinking problems to seek help and to be referred for treatment at earlier stages than previously. Macrae et al speculate upon the possibility that '...the total pool of alcoholics has remained unchanged, and that the various figures ...demonstrate primarily the increasing enthusiasm of both alcoholic and psychiatrist for admission to hospital for in-patient treatment.' As will be seen later, if treatment is to be given at all, then the geography of much of Scotland is such that in-patient care is the only possibility. The reality is almost certainly that all three factors above are involved in creating the elevated figures for alcoholism and alcoholic psychosis in Scotland. In other words, alcoholism etc. probably did increase

in real terms throughout the 1960s, partly in response to the price of alcohol lagging behind the rise in price of other commodities and partly in response to severe unemployment (Kendell et al, 1983; Killich and Plant, 1982); doctors and patients probably became more aware both of the need for treatment and of the improved chances of success; having decided upon treatment, hospitalisation (as opposed to attendance at day clinics) was the only course available.

As noted above, the national rate for alcoholism and alcoholic psychosis in Scotland was 36.1 per 100,000 in 1977; this was more than four times the rate in England and Wales at the time. Admission rates in the Highlands and Western Isles were more than double those for any other Scottish region and nearly ten times more than the highest rates in England (Killich and Plant, op cit). Crawford et al (1984), suspecting - as Macrae had earlier - that such high admission rates were not a reliable indicator of alcohol abuse, conducted a two-fold enquiry. They set out first to establish general consumption levels and drinking patterns in three areas with widely differing profiles of alcohol-related problems - the Highlands, Tayside and Kent. The authors then interviewed a group of patients whose primary diagnosis had been one of 'alcoholic psychosis' from each of the three areas; this was to determine whether there were any regional differences in consumptions, or in resultant problems, which might explain the differences in admission rates. In a sample of 2,349 persons (1,413 males,

932 females) drawn at random from electoral registers, Crawford et al found that the proportion of abstainers in the Highlands was approximately double those in the other two areas. Highlanders were also significantly less likely to have drunk alcohol during the week preceding the interview. Among drinkers there was a significant difference between the Highlands and Tayside in the mean levels of alcohol consumed in the pre-interview week: males in Tayside drank the most, in the Highlands both sexes drank the least. However, when consumption levels from all three regions are compared with the corresponding psychiatric admission rates it can be seen that the Highlands - with the lowest consumption levels - have an overall admission rate twelve times that of Kent, where consumption levels are actually higher than in the Highlands (see below).

TABLE Mean levels of self-reported alcohol consumption (in units) in three areas.

	Highlands	Tayside	Kent
Males	15.4	19.2	16.9
Females	5.5	6.7	7.3
First admissions to psychiatric beds, rates per 100,000 population.			
Both sexes	.75	.62	.06

Source: Crawford et al, 1984

In the second part of their study, Crawford et al interviewed three samples of in-patients with an alcohol-related problem (N = 100 (Highlands), 90 (Tayside), 50 (Kent)). Summarising their results Crawford et al write: 'These samples did not differ either in relation to measures of alcohol consumption, dependence or measures of alcohol-related problems in health, family or public order in such a way as to support the view that admission rates might be higher in the north of Britain because individuals were admitted who were less severely alcohol-dependent or with fewer problems. However...when outpatients and day patients are taken into account, together with those treated in medical beds (with no double counting), the twelvefold difference almost disappears.' In other words, the differences in the total numbers of people being treated for alcohol problems, as distinct from those occupying beds for the same reason, is not significantly different between the three areas. The impression of disproportionately high rates of alcoholism and alcoholic psychosis in the north of Scotland is the result a) of using bed occupancy as the main index of harm, and b) a failure - until the work of Crawford et al - to appreciate that the geography of the Highlands, with large distances and difficult communications, precludes day care; the difference is one of admissions policy, not incidence.

3.5.3 Mortality from 'alcoholism'

Although alcoholism, alcohol dependence and alcoholic psychosis (ICD numbers 303, 303.2 and 291, respectively) are listed as causes of death in UK mortality statistics, the numbers of deaths recorded under these headings should be regarded with some scepticism. Adelstein and White (1976) have reviewed the causes of death among alcoholics: these include accidents, suicide and violence, cirrhosis of the liver, various cancers and respiratory diseases. On death certificates the immediate cause of death is often the only one mentioned, contributory causes - such as the role of alcohol in causing an accident - are frequently omitted. A further problem (see Wilkins, op cit) is created by the unwillingness of some doctors to use the terms 'alcoholic' and 'alcoholism' on official returns. Taken together, these factors result in a degree of under-reporting which impairs the quality of alcoholism statistics to the point where the data are of limited use to the epidemiologist. For this reason no attempt has been made here to correlate alcoholism mortality with mortality from oesophageal cancer.

3.5.4 Alcohol-related crime in Scotland

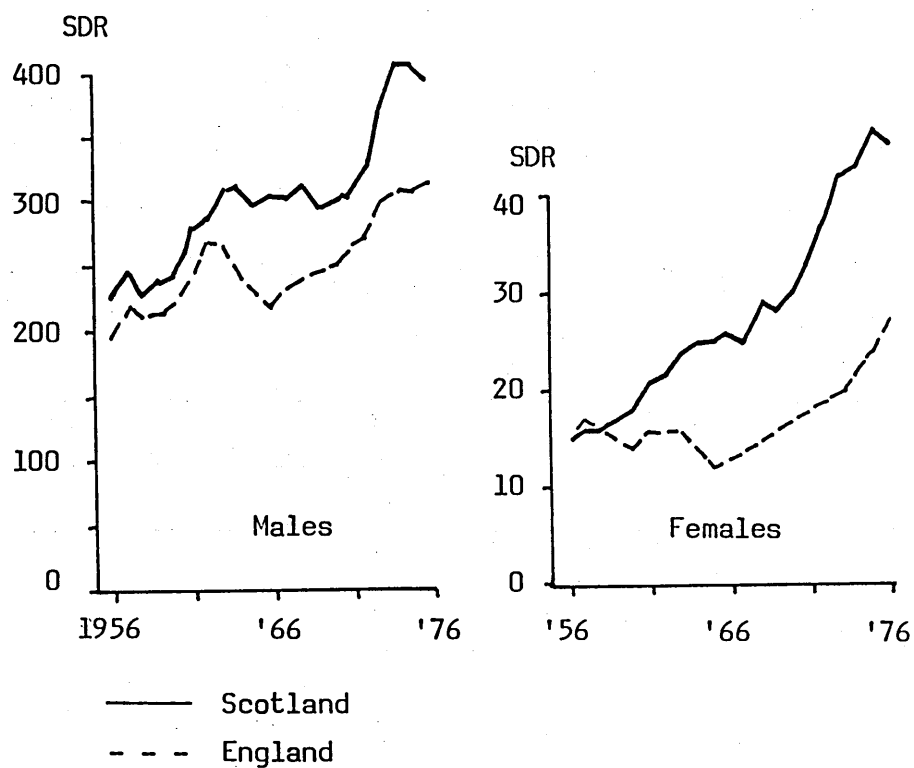
Alcohol-related crimes are classified differently north and south of the border. Scottish offences are: being drunk and incapable, drunk in charge of a child or motor vehicle, and offences relating

to drunken driving. In England and Wales offences are described as: drunkenness in a public place or licensed premises, drunkenness with aggravation, and offences related to drunken driving. Some authors have used arrests for drunkenness alone as an indicator of alcohol abuse (Haskey et al, 1983), while others have aggregated data for drunkenness, drunken driving and other offences to form a composite index (Killich and Plant, 1981). Differences of crime definition, and in treatment of crime data, mean that surveys are seldom strictly comparable. There are other problems: English and Welsh official statistics record convictions, Scottish statistics are for alcohol-related crimes 'known to the police' (for which latter the conviction rate is about 82% (Killich & Plant, op cit)). More seriously, the recording of crimes of drunkenness or of driving while under the influence of drink depends on police staffing numbers and vigilance; if there is no policeman to witness the offence, there may be no prosecution and no resultant statistic. Such variables limit the usefulness of alcohol-related crime as an index of alcohol abuse.

The above caveats should be borne in mind when reading the following: Haskey et al (op cit) produced standardised drunkenness ratios (SDRs) for each of the countries of the UK, and for the fifteen Regional Health Authorities of England and Wales; regional variations within Scotland were not examined.. Data in Haskey et al show that there is a ten-fold difference between the ratios for

FIGURE 6

Trends in drunkenness offences
Standardised drunkenness ratios (SDRs*)
Scotland and England 1956 - 1976



*SDRs standardised on 1956 England and Wales person
drunkenness rates Source: Haskey et al (1983)

males and those for females, although females were involved in a proportionally greater rise in drunkenness offences over the period 1956-76 (see Fig. 6 on facing page).

Killich and Plant (op cit) - using a composite index - found that the rates of alcohol-related crime in the twelve Scottish regions were all higher than in the nine English and Welsh regions.

Overall, the national rate of such crimes in Scotland was 1536.2 per 100,000 population; 4.7 times the national rate in England and Wales. Even reducing the figures to include eventual non-convictions, the Scottish rate is still 3.8 times the rate in England and Wales.

TABLE Alcohol-related crime in Scotland: incidence and rates per 100,000 population, by region, both sexes.

Region	N	Rate/100,000
Highland	2,178	1147.5
Shetland	212	1039.2
Western Isles	255	858.6
Tayside	2,693	669.9
Strathclyde	15,436	625.9
Grampian	2,695	587.3
Lothian	3,311	437.8
Orkney	76	422.2
Central	972	357.9
Dumfries & Galloway	423	295.0
Fife	920	271.2
Borders	253	252.0

Source: Killich and Plant (1981)

The preceding table shows that the Highlands, Shetland and the Western Isles have the highest rates of drunkenness and associated crime in Scotland. This is in striking contrast to what is known about alcohol consumption levels in these areas. The Highland region - with the highest rate of alcohol-related crime - has the lowest per capita consumption rates in Scotland (see section 3.4.2). Alcohol-related mortality in the three northernmost regions is also very low, though this may in part be due to under-reporting. Killich and Plant (op cit) believe that the apparent pattern of mortality '...may reflect local practices of recording deaths, rather than a genuine absence of deaths from such causes.' Errors in death registration have already been mentioned in connection with the Cancer Registry (*vide* Crossfill, 1973 - section 2.1.4), and some at least of the reasons for failing to register cancer deaths may also apply to deaths from cirrhosis and other alcohol-related causes.

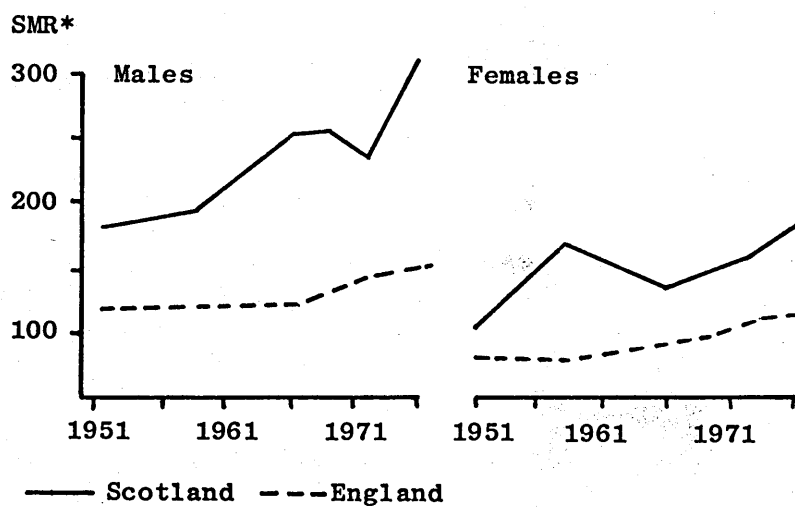
Alcohol-related crime appears to be negatively correlated with cancer of the oesophagus in the three northern areas, although the populations are so small that cancer rates are very unstable and apparent variations are just as likely to be due to error variance as to any real differences in mortality rates. Taking all twelve Scottish regions and comparing the two alcohol-related variables - crime and oesophageal cancer - the author found no correlation at all ($r = .08$).

The reasons for the very high rates of alcohol-related crime in northern Scotland may in part be due to social and cultural factors, e.g. abstinence during the week and 'binges' at the weekend, and perhaps a tolerance - among males at least - for public displays of drunkenness or drink-related aggression. Drunkenness may also be associated with very high levels of unemployment, though Killich and Plant found a higher correlation between unemployment and admissions for alcoholism and alcoholic psychosis. The Western Isles, with 13.3% of the populace unemployed, and the Highlands, with 9.1% unemployed (1977 figures), are among the worst unemployment areas in Scotland. Whatever the reasons for the high rates of drunkenness, however, the use of this index to throw light on other alcohol-related conditions (e.g. oesophageal cancer) clearly has no value whatever.

[In passing: Road accident data are not used as an indicator of heavy drinking prevalence. Although there are detailed road accidents statistics by county, and although there is a strong correlation between alcohol use and road accidents (see, for example, Coddling and Samson, 1974; Clayton et al, 1975; Denney, 1979 and RoSPA, 1983) and, further, although there is a direct, proportional relationship between injury severity and blood alcohol concentration (Irwin et al, 1983), road accident statistics are poor indicators of heavy drinking prevalence: statistically, it is difficult or impossible to control for other variables such as poor visibility, road surface conditions,

FIGURE 7

Trends in cirrhosis SMRs: Scotland and England: 1951-1976



*SMRs standardised on 1951 rates for England and Wales (smoothed data)

Source: Haskey et al (1983)

mechanical failure and the behaviour of other road users.]

3.5.6 Cirrhosis mortality in Scotland

In the years 1957-76 the highest SMRs for cirrhosis among males in the UK occurred in Scotland: rates for males were from one and a half to twice those for females in each county (Haskey et al, 1983). Within Scotland cirrhosis death rates exhibit some peculiarities. For example, in some years there is a virtual absence of cirrhosis deaths recorded in the Western Isles and Shetland, this despite the apparently high rates of alcohol-related crime and hospital admissions for alcoholism. Given that cultural and geographical factors may combine to give an exaggerated impression of drinking levels in these areas, one would still expect to see some cirrhosis deaths in most years. As previously suggested, 'local practices' of recording deaths may be responsible for the anomalously low cirrhosis rates in these areas. The sexes also exhibit marked differences in cirrhosis mortality over time, as the figure on the facing page shows.

For Scottish males the steep rise in cirrhosis mortality was interrupted only once during the 25 year period shown above, when a sudden, sharp fall occurred between 1967 and 1973. It is unfortunate that this solitary dip in the male death rate overlaps with the period from which the oesophageal cancer data used in this study are taken. The small number of cirrhosis deaths

between 1967 and 1973, and the likelihood of unstable rates in some areas, may affect the validity of the correlation test between cirrhosis and oesophageal cancer (discussed below).

Another factor makes it difficult to draw useful inferences from any correlation exercises involving Scottish cirrhosis rates: between 1971 and 1981 the proportion of cirrhosis deaths attributed to alcohol increased substantially (see below). There is little possibility of misdiagnosis being responsible for the small proportion (9.6%) of alcohol-related cirrhosis deaths recorded in 1971; diagnostic techniques for this disease are very reliable and have been for a number of years (Latcham, personal communication, 1984).

TABLE 14 Cirrhosis deaths in Scotland in 1971 and 1981
Males - rates per 100,000 population

	1971	1981
alcoholics	0.5 (9.6%)	4.5 (42.9%)
non-alcoholics	4.7	6.0
total	5.2	10.5

Sources: Annual Reports of the Registrar General for Scotland

From the rather low death rates shown above it might be supposed that descriptions of Scottish alcohol consumption and its harmful consequences had been exaggerated. However, the comparative rarity of cirrhosis does not necessarily indicate a small

Apropos sections 3.5.7 and 3.5.8

At this point the author departs from conventional literature survey practice and uses some of the study data to explore the alcohol/cirrhosis/cancer association in Scotland: more than that, an attempt is made to develop an hypothesis which might explain the observed association. The reason for the unconventional approach is that the alcohol/cirrhosis/cancer relationship - if it exists - is so complex that, in the author's view, the issues become easier to follow if literature, data and arguments are marshalled together in one section.

population of drinkers, but rather reflects the small proportion of drinkers whose consumption is high enough to cause liver damage (and the fact that some very heavy drinkers appear to avoid cirrhosis, while others who get cirrhosis may miss being recorded). The much larger proportion of moderately heavy drinkers - who avoid cirrhosis - probably contribute to the somewhat higher rates for oesophageal cancer.

TABLE Oesophageal cancer deaths - Scotland
Crude rates per 100,000 population

	1970-72	1980-82
Males	8	12
Females	7	9

Sources: Annual Reports of the Registrar General for Scotland

The dip in the cirrhosis death rate for males during the period 1967-73 and the changing proportion of cirrhosis deaths attributed to alcohol should be borne in mind when studying Fig. 8 and the supporting data in Table 15.

3.5.7 Correlation of cirrhosis with oesophageal cancer in Scottish males*

i) Selection of areas

Twelve representative areas were chosen for this exercise: the four cities, four of the large burghs and four of the rural-area groupings used in analysing the spatial distribution of oesophageal

* See note on facing page.

TABLE 15

LIVER CIRRHOSIS AND OESOPHAGEAL CANCER IN SCOTLAND: CORRELATION TEST FOR TEN SELECTED AREAS: MALE SMRS:
(Cirrhosis data 1970-73, oesophageal cancer data 1970-74.)

Areas	Oesophageal cancer SMR	Cirrhosis SMR
Dundee CC [#]	156	94
Banff, Moray & Nairn RG	142	82
Greenock LB	138	47
Edinburgh CC	114	108
Glasgow CC	104	153
Aberdeen CC	96	85
Paisley LB	88	167
Motherwell & Wishaw LB	87	133
Lanark DC	71	105
Dumfries, Kirkcudbright & Wigtown RG	55	131

* For selection criteria see text on facing page

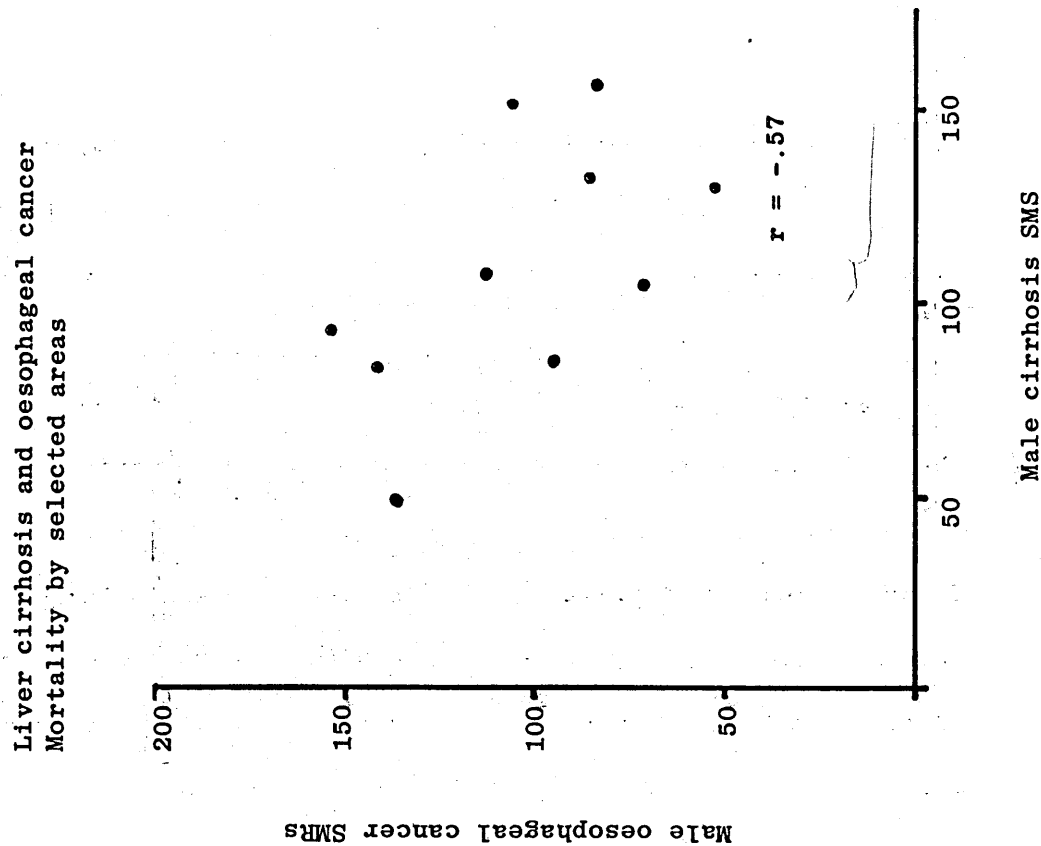
[#] CC = City of County LB = Large Burgh

DC = District of County RG = Rural Grouping

Sources:

Cirrhosis data: Registrar General's Annual Reports
Oesophageal cancer data: computer tabulations
supplied by the General Register Office for Scotland

FIGURE 8



cancer deaths (see Chapter 7). Apart from the cities, which together contain about 35% of the Scottish population, areas were selected using two criteria: a) each group should contain examples of high and low oesophageal cancer SMRs against which to compare cirrhosis SMRs, and b) none of the study populations should be less than 30,000 - a figure designed to minimise the effects of random 'noise'. None of the New Towns was selected (apart from East Kilbride, which was also a pre-1974 large burgh) as the majority had male populations of 20,000 or less in 1971. East Kilbride was later excluded, along with the rural-area grouping of Caithness, Ross & Cromarty and Sutherland, partly because the number of cirrhosis deaths proved too small for any reliance to be placed in the SMRs, but also - in the case of the rural areas - it emerged that there were grounds for doubting the reliability of cirrhosis-death reporting in the Highland area (Killich and Plant, 1981). Oesophageal cancer data are for the years 1970-74 and were supplied by the General Register Office for Scotland. Data on cirrhosis deaths by local government area are from the Annual Reports of the Registrar General for Scotland, 1970-73.⁸

ii) Discussion of results

On the basis of the results from the ten selected areas, the relationship of cirrhosis to cancer of the oesophagus in Scottish

8. From 1974 age-specific deaths are not given by local government area but only for the much larger Health Board or Health District areas.

TABLE 16

Intercorrelations of three types of alcohol-related mortality with alcoholism and alcoholic psychosis: 1977 data, male and female combined.

Intercorrelation type	England & Wales	Scotland
Alcoholism and alcoholic psychosis : cirrhosis	+.79	+.27
Suicide, self-inflicted injury and accidental poisoning : cirrhosis	+.58	-.44
Suicide, self-inflicted injury and accidental poisoning : alcoholism and alcoholic psychosis	+.45	-.19

Source: Killich & Plant (1981)

males appears to be the opposite of that found among males in England and Wales (Chilvers et al, 1979), France (Pequignot, 1977) and Australia (McMichael and Hetzel, 1975). Whereas Chilvers et al found a strong and positive correlation ($r = .66$) between the two causes among men in the nine standard regions of England and Wales, the present author finds a moderately strong but negative correlation ($r = -.57$) among males in Scotland. This result, though puzzling, is at least consistent with other Scottish alcohol-related trends, most of which - as Table 16 shows - have a disconcerting habit of running counter to those seen in England and Wales.

It has been argued that statistical or visual analysis of geographical data yields results which are entirely scale-dependent (Rhind, 1975), so that it is possible that differences in the strength (and even the sign) of the relationship between Scottish variables and their counterparts elsewhere are no more than statistical artifacts, the products of small population size. However, all of the population units used by the author to test the relationship between cirrhosis and oesophageal cancer have contained more than 30 000 persons: five areas had more than 80 000 persons. These units are comparable in size with those used by workers in, for example, Australia, Norway and Brittany,

where positive relationships between oesophageal cancer and cirrhosis have been observed. If statistical artifacts are not to blame, then there is no ready explanation for this tendency of Scottish alcohol trends to be the reverse of what would be normally expected and - in the case of cirrhosis and cancer of the oesophagus - there seems to be no hypothesis capable of satisfying all of the conditions generated by the correlation results; this is particularly the case if alcohol is assumed to be the common factor linking the two diseases.

One possible explanation, which cannot yet be tested because of the lack of systematic data on regional alcohol consumption, draws on Pequignot's ideas of a 'comparative natural history' of delirium tremens, cirrhosis and oesophageal cancer. According to Pequignot the highest-category chronic drinker (80g ethanol a day plus) is likely to die of delirium tremens around the age of 45. In the next highest category (60-80g/day) the individual would be at risk of developing cirrhosis at about 55 years, while those in the next category down (40-60g/day) would have an increased risk of oesophageal cancer in their late 60s. Before Pequignot's idea can be invoked, however, it is necessary to propose the existence in Scotland of marked regional variations in alcohol consumption: variations both in average consumption levels and in the composition of the drinking population. It is known that such variations exist, indeed, it is known that

significant variations in drinking and smoking habits can occur in towns only a few miles apart (Plant and Pirie, 1979; Cummins et al, 1981); unfortunately, the information currently available is only fragmentary.

In the 'Pequignot model' an area with a high SMR for cirrhosis but a low SMR for oesophageal cancer would have a drinking population characterised by a majority of light drinkers, a few in the intermediate category, and an above-average population of chronic heavy drinkers. In such an area the chronic heavy drinkers would be exposed to increased risk of early death from delirium tremens, suicide and other alcohol-related self-harm, and from cirrhosis.

The majority of drinkers, by virtue of their moderate drinking habits (the moderation would probably also apply to smoking) would tend to avoid cirrhosis and cancer of the oesophagus as well.

In the reverse situation, that of an area with a low cirrhosis SMR and a high oesophageal cancer SMR, there would be a larger proportion of moderate to heavy drinkers, with only a small fraction of drinkers falling within the topmost consumption category and likely to die from delirium tremens or cirrhosis.

The highly skewed consumption pattern proposed for the area with above-average cirrhosis mortality, and the less skewed consumption pattern proposed for the area with elevated oesophageal cancer rates, happen also to tally with the model proposed by Lederman (op cit, section 3.3.1) to describe the distribution of drinkers

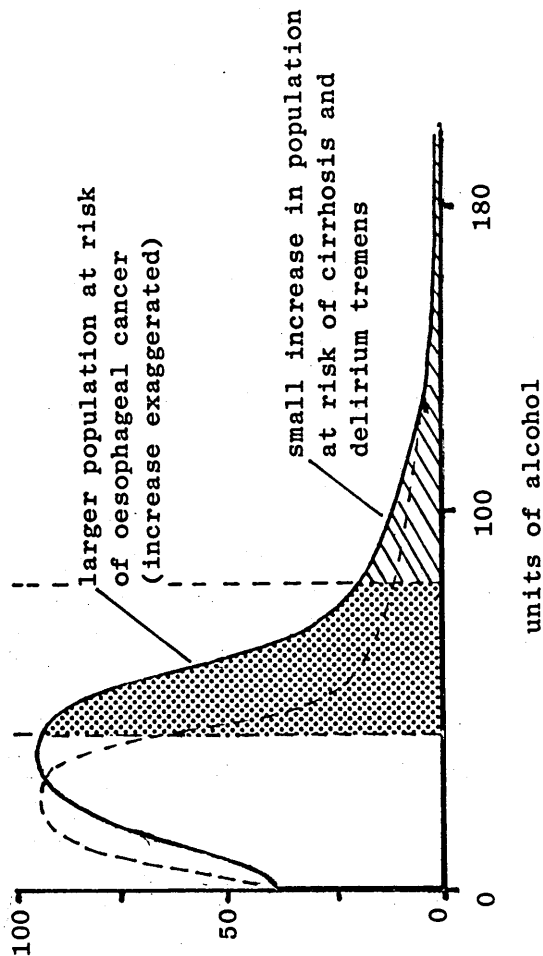
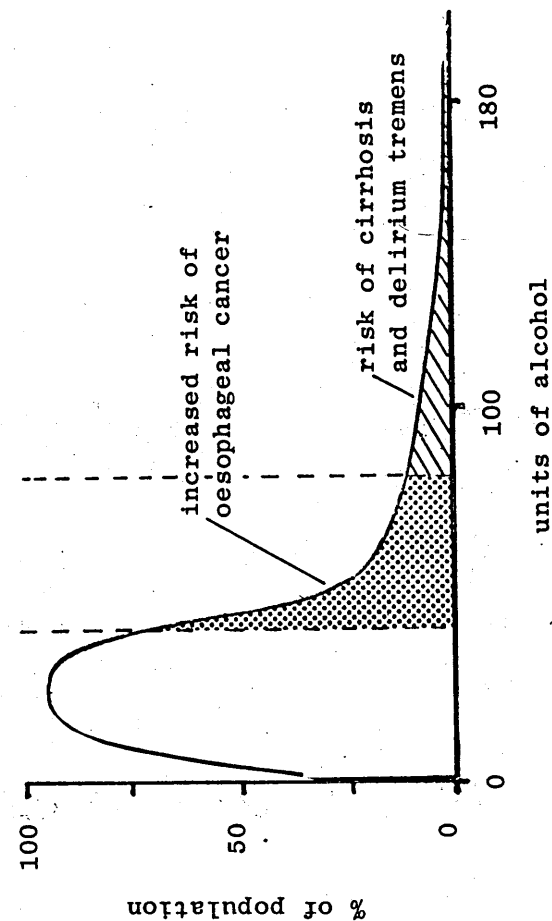
SCHEMATIC REPRESENTATION OF TWO DRINKING POPULATIONS

FIGURE 9

2: HIGH per caput consumption

1: LOW per caput consumption
(NB: Populations at risk not drawn to scale)

>>>>> Consumption shift >>>>>



at different levels of per caput consumption. At low per caput levels the great majority of drinkers, probably more than 90%, fall into the light to moderate category; under 10% will be moderate to heavy drinkers and 1% or less will be very heavy drinkers. As consumption levels rise (e.g. in response to a fall in the real price of alcohol) it would be expected, according to Lederman, that a proportion of drinkers who had been in the light to moderate category would increase their consumption and move into the moderate to heavy category; in so doing the proportion of people at risk from cancer of the oesophagus would also increase; the idea is shown schematically on the facing page.

A problem (one of several) arises at this point: assuming that an increase in overall consumption results in the predicted redistribution of drinkers and, moreover, in a larger number of people being exposed to the risk of oesophageal cancer, what happens in the highest consumption category? According to Lederman's predictions, although the number of pathologically heavy drinkers would increase by only a tiny amount, those in that group would be likely to drink even more, thereby enhancing their already high chances of dying from cirrhosis and other early-onset manifestations of alcohol abuse. If alcohol is the common factor linking cirrhosis and oesophageal cancer, and if Pequignot is correct in his analysis of the relationship between consumption levels and the nature and age of disease onset, then we should certainly

expect to find above-average oesophageal cancer rates in high consumption areas. However, because drinkers in the top consumption category would also have increased their chances of dying from cirrhosis, we should expect to find above-average rates for this disease as well. SMRs in such areas would tend to move in parallel and not diverge; as they seem to in Scotland. In short, the model seems to offer an explanation of how oesophageal cancer rates might vary with changing levels of alcohol consumption, but it does not offer a satisfactory explanation of the cirrhosis rates as observed in Scotland.

A further problem arises concerning the elevated SMRs for cirrhosis in low oesophageal cancer areas. For the oesophageal cancer SMR to be low but the cirrhosis SMR high, one must postulate a situation in which - while the majority of drinkers consume modest amounts - the proportion of very heavy drinkers is higher than is found elsewhere. This further condition imposed upon the argument would appear to strain it to breaking point, yet there are grounds for suggesting that some Scottish areas may in fact have a higher proportion of problem drinkers. Attention has already been drawn to the fact that for some indices of alcohol-related harm, such as drunkenness and hospital admissions for alcoholism and alcoholic psychosis, rates in the Highlands and Islands are far higher than elsewhere. Even allowing for the extra provision of hospital beds and for

variations in police surveillance levels - both of which may raise these indices above normal - there are elevated rates for other indices (e.g. suicide, accidental poisoning and self-inflicted harm) which point to a higher than average concentration of problem drinkers. The explanation for this higher fraction of aberrant drinkers is not immediately apparent. The Highlands and Islands have some of the highest unemployment rates in Scotland, but whereas unemployment and alcohol-related mortality are highly correlated in England and Wales ($r = .73$), in Scotland they are, once again, negatively correlated ($r = -.62$) (Killich and Plant, op cit). The answer, whatever it is, is not to be found in so simple an association as an alcoholic response to the stress of unemployment.

Chronic alcohol abuse has a well-documented psychopathological element, it has even been described by some writers in terms of protracted suicide or 'parasuicide' (Kreitman, 1977; Ritson, 1977). It seems clear that the number of pathological drinkers in a population is determined primarily by factors other than unemployment or the relative price of alcohol, though these may be important secondary influences on susceptible individuals. In essence, it is argued here that some areas have higher cirrhosis levels than others because they have a higher proportion of pathological drinkers. It is of course true that variations in the real price of alcohol have a crucial bearing on consumption:

time and again it has been shown that when the real price of alcohol falls - either relative to rising incomes or because of a reduction in taxation (duty) - consumption rises and with it all indices of alcohol-related harm. Conversely, when the relative price of alcohol goes up, consumption falls and so do all the indices of harm, even including deaths among the most seriously addicted and impaired drinkers (in Scotland a fall in alcohol-related morbidity and mortality following a rise in excise duty has been recently documented by Kendell et al, 1983).

However, it is argued that the main body of chronic drinkers in any area is composed of people who are predisposed to self-destructive behaviour, and whose impulses happen to be given expression - and are perhaps exacerbated - by alcohol. Factors known to be associated with this type of self-destructive behaviour include lack of success in work, inability to cope with stress, poor self image and loneliness; particularly at risk are the single, divorced and widowed, especially if poorly educated and/or of low socio-economic class. There are grounds for suggesting that some areas of Scotland may have a somewhat higher proportion of persons matching these descriptions than elsewhere.

Historically, the north of Scotland has experienced a steady outflow of the physically and intellectually able seeking

opportunity elsewhere. For those left behind, rural occupations in remote areas carry the prospect of toil, isolation and poor chances of meeting a suitable partner. Fishing and other occupations connected with the sea are also important in the economy of the north, and were more so 25 years ago. Sea-related occupations carry a notoriously high risk of alcoholism and may in fact attract people with drinking and other psychological problems (Rix et al, 1982). Such factors may explain why the Highlands and Islands appear to have a higher than average proportion of aberrant drinkers. Paradoxically, the depressed economy of the region may be one reason for the relatively modest consumption of the majority (described by Crawford et al, 1984); though alcoholics will almost always find the means to satisfy their addiction, most people in the north would not have the money to spend on large amounts of alcohol.

In circumstances such as those described above it is possible to see that an area could produce the unusual combination of a heavy-drinking minority with an above-average cirrhosis rate, and an abstemious or light-drinking majority with a low rate of oesophageal cancer. The reverse situation - low cirrhosis/high oesophageal cancer - might be explained in terms of a basically prosperous area where the majority of drinkers could afford to indulge their preferences, while yet avoiding the descent into a pathological drinking state. It could even be argued that the conditions favourable to the emergence of substantial numbers of self-

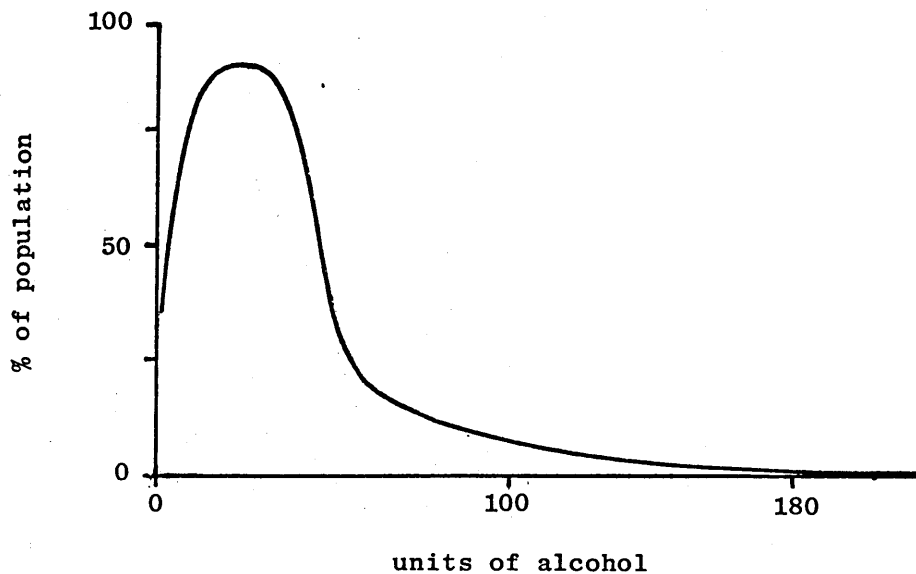
destructive drinkers might be absent or minimal in the economically better-off areas. In practice, though, it is possible to accept the first example, it is difficult to argue a convincing case for the second. If the Lederman theory is empirically correct, as it seems to be, a rise in gross consumption would be reflected in an overall shift of drinkers into heavier consumption categories. To be sure, there would be an increased number of moderately heavy drinkers who would probably contribute to higher levels of oesophageal cancer, but consumption in the higher categories would also increase, with the near certainty that cirrhosis levels would rise. The effect would be of cirrhosis and oesophageal cancer rates moving in parallel, rather than in contrary motion, as observed. This attempt to fuse ideas from Pequignot and Lederman, with what is known or may be deduced of conditions in parts of Scotland, is inadequate to explain the relationship between cirrhosis and oesophageal cancer in the Scottish context.

3.5.8 Coda

Having argued the case for the existence of 'pathological' drinkers, it must be said that consumption surveys consistently fail to reveal any such group. Typically, a consumption survey will produce a result similar to the following:

FIGURE 10

Distribution of drinkers (and non-drinkers) in a 'typical' population.

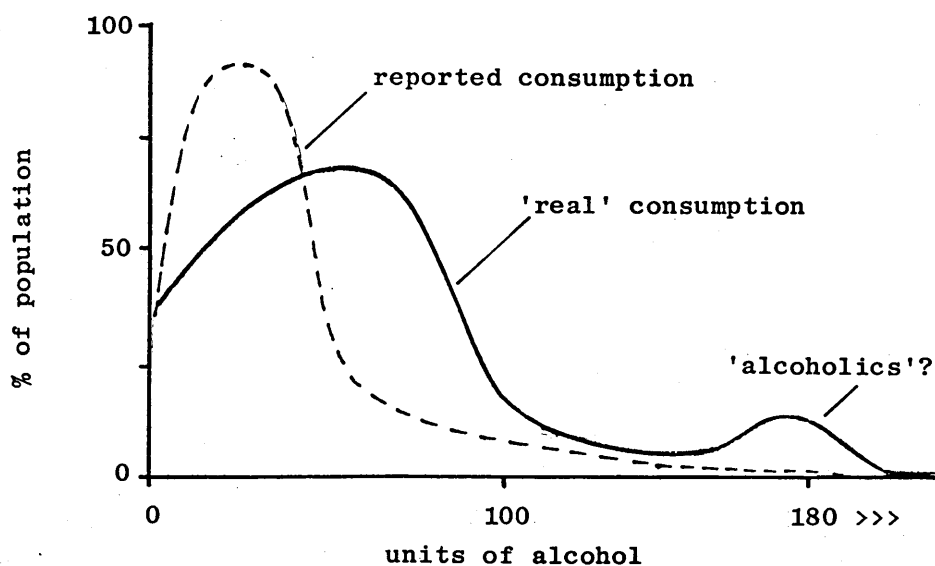


The curve shows that the bulk of drinkers fall into the 'light' category, with fewer and fewer people in each of the ascending consumption categories. If such results are to be believed, then - so far as their intake is concerned - 'alcoholics' are merely those at one end of a distribution curve. However, there are very good grounds for doubting the accuracy of such surveys: to begin with there exist, in psychiatric hospitals and detoxification units throughout the country, thousands of individuals whose drinking behaviour has placed them at risk and must clearly be regarded as aberrant. There is also the well-documented fact that the higher their real intake the greater the likelihood

that people will under-estimate or actually lie about their drinking. It follows from this last that the most inaccurate part of any survey will be that concerned with the heaviest drinkers at the tail end of the drinking curve. Plant (1979b) suggests that, were surveys ever to get completely truthful information, the resultant curve would probably be bi-modal, as shown below:

FIGURE 11

Hypothetical 'real' consumption in a drinking population



It may well be that the Highlands and Islands drinkers - if data permitted - would fall into just such a consumption curve.

CHAPTER FOUR: THE SEARCH FOR AETIOLOGICAL AGENTS: TOBACCO,
ORAL HYGIENE AND EDENTIA

Contents

- 4.1.0 Introduction
- 4.1.1 Tobacco and alcohol as independent risks
- 4.1.2 Tobacco and alcohol: combined risks
- 4.1.3 Tobacco, alcohol and cancer site
- 4.2. Possible mechanisms
- 4.3. Patterns of tobacco consumption in Scotland; the limited evidence
- 4.4. Oral hygiene and edentia
- 4.4. Edentia in Scotland.

CHAPTER FOUR: THE SEARCH FOR AETIOLOGICAL AGENTS: TOBACCO, ORAL HYGIENE AND EDENTIA

4.1.0 Introduction

While most epidemiologists agree that tobacco is a principal agent in cancers of the buccal cavity, larynx and pharynx, its role in cancer of the oesophagus is still controversial. Some believe that in the absence of alcohol, tobacco poses an insignificant risk of oesophageal cancer (for example: Berg, 1975; Keller, 1980). Others regard the alcohol effect as entirely dependent upon tobacco consumption (for example: Feldman and Boxer, 1979; Rothman et al, 1980). The evidence is conflicting and seems to vary with the type of study. Case-control studies generally show a clear gradient of risk between tobacco consumption and oesophageal cancer, even when the investigators have controlled for alcohol. Contrasting evidence, however, comes from cross-racial studies in which, for example, it is shown that American whites - who smoke more than blacks - have lower oesophageal cancer rates than American blacks, who in turn drink far more whisky than whites (Keller, 1980). Autopsy studies lend support to a causal role for tobacco: marked histological differences have been detected between the oesophagi of non-smokers and smokers, with the latter showing signs of epithelial thickening (hyperplasia) and damaged cell nuclei, both of which may be precursors of cancer (Auerbach et al, 1965; Warwick and Harington, 1973). On the other hand, cohort studies do not reflect a close

correspondence between tobacco consumption and cancers of the lung and oesophagus (McMichael and Hetzel, 1978; Chilvers et al, 1979). Moreover, in a number of countries where alcohol consumption is minimal or non-existent (e.g. Iran, Northern China and some Indian states), studies have failed to show a strong correlation between tobacco and cancer of the oesophagus (Mahboubi et al, 1973; Cook-Mozaffari et al, 1979; Kaplan and Tuschitani, 1978; Yang, 1980; Jayant et al, 1977). An increasingly accepted point of view is that alcohol (a) and tobacco (t) interact synergistically to elevate the relative risk (RR) of oesophageal cancer far above the levels posed by either risk factor on its own, or even added together. Tuyns (1982) proposes a straightforward multiplicative model, expressed simply as $RR_{at} = RR_a \times RR_t$. The mechanisms discussed in section 4.2.1 below involve alcohol as an indispensable agent in mediating or potentiating the effects of tobacco carcinogens.

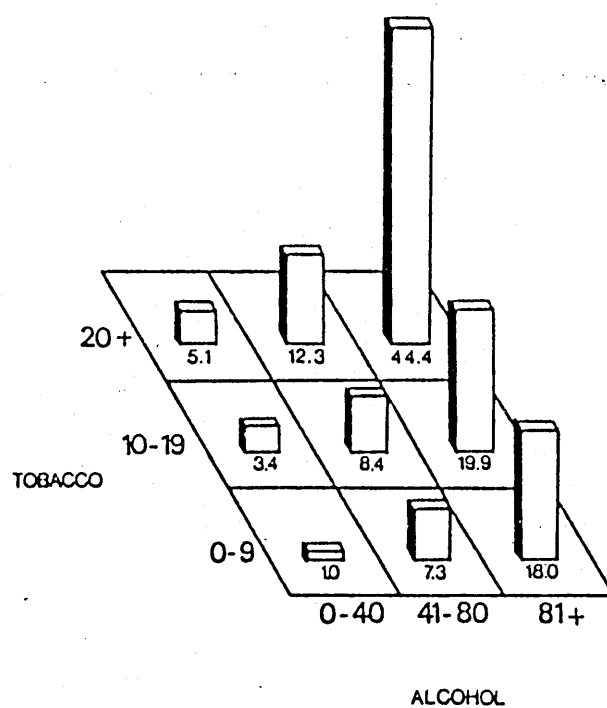
4.1.1 Tobacco and alcohol as independent risks

In an early paper, Wynder and Bross (1961) asserted that tobacco on its own carries a very low risk of oesophageal cancer. They were influenced in this conclusion by the fact that there has been no rise in oesophageal cancer rates in the Western world to match the huge rise in tobacco consumption and in lung cancer. However, Wynder and Bross qualify their conclusion by pointing out that pipes, cigars and chewed tobacco present a greater risk of oesophageal cancer than cigarettes, and that while cigarette consumption

has increased steadily since the beginning of the century, pipe and cigar smoking have declined; had these kept pace with cigarette consumption the time trends might show a closer link between tobacco and oesophageal cancer. Keller (1980) looked at oesophageal cancer rates in black and white Americans and found that although whites smoke significantly more than blacks, they have less than a third of the death rate. Keller believed that the elevated rate in his group of black patients was due to their high consumption of whisky. He (Keller) concluded that: '...alcohol beverage consumption entails a significantly high risk of oesophageal cancer, which is independent of smoked tobacco...[indeed]...on controlling for alcohol consumption the risk of oesophageal cancer is not significantly high' (emphasis added). Feldman and Boxer (1979) arrived at the diametrically opposite conclusion, as did Wynder and co-workers in later studies. Wynder et al (1975) took the view that '...cigarettes, pipe tobacco, cigars and chewing tobacco represent the principal stimulus for the development of cancer [of the upper alimentary tract].' More than that: 'Our studies have indicated that, while tobacco use alone can lead to cancer in those regions, heavy intake of alcohol by itself does not lead to such carcinogenic activity.' (Wynder and Bross, op cit.) In fact, data published by both opposing groups of authors show that their samples included oesophageal cancer patients who were drinking non-smokers or smoking non-drinkers. Clearly each substance on its own can present an oesophageal cancer risk, particularly at heavy consumption levels. Equally clearly,

FIGURE 12

Cancer of the oesophagus: relative risk
in relation to daily consumption of
alcohol and tobacco (in grams per day).



Source: Pequignot et al (1977)

though either substance may influence the development of this cancer, neither is essential to the process (though without either, as Tuyns et al (1977) point out, the risk in Western countries is 'excessively low').

4.1.2 Tobacco and alcohol; combined risks

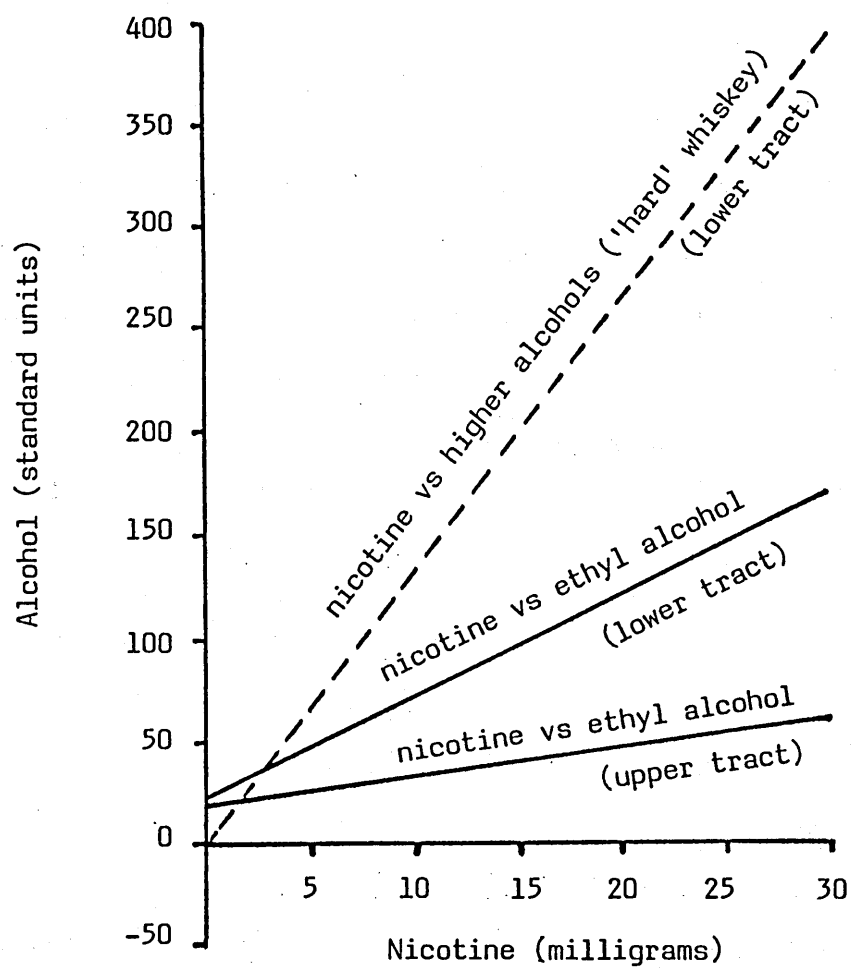
Tuyns et al (op cit) plotted the dose-response relationship of each substance against the other, held at constant levels; there was a clear dose-response for tobacco after adjustment for alcohol, and for alcohol after adjustment for tobacco. Tuyns et al regarded this as evidence that either substance could play a role independent of the other, although their independent roles were minor in comparison with the risks engendered by consumption of both substances together. The often reprinted 'three dimensional' figure by Pequignot et al (1977) (see facing page), admirably shows the double gradient of the combined risks. McCoy et al (1980), produced similar diagrams, showing comparable gradients of risk, for cancers of the buccal cavity and larynx. They did not, unfortunately, include a diagram for cancer of the oesophagus.

4.1.3 Tobacco, alcohol and cancer site

Kissin (1975) attempted a more refined analysis of the roles played by alcohol and tobacco by relating the amounts drunk and smoked to the cancer site. Kissin hypothesised that, in cancers of the

FIGURE 13

Regression equations for nicotine and alcohol and cancers of the upper and lower aerodigestive tract.



Source: Kissin, 1975 (simplified).

'head and neck', smoking should play a larger role in cancers of the 'inhalation tract'. Thus, among individuals who smoke more than they drink, cancers of the roof of the mouth, mesopharynx, larynx and lung should predominate: those who drink more than they smoke should display more cancers of the floor of the mouth, the hypopharynx and the oesophagus. In short, the site of the cancer reflects the contact surface of the smoke or alcohol. In the (simplified) diagram from Kissin (op cit), regression slopes are plotted for nicotine versus ethyl alcohol in cancers of the upper (inhalation) tract, and lower (ingestion) tract (see Figure 13 on the facing page).

Kissin points out that in the 'lower tract' the ratio inclines more towards alcohol, whereas the 'upper tract' line inclines more to nicotine. Kissin regards this as evidence that the site of the cancer is related to the directness of contact of either alcohol or tobacco smoke. It is not always possible, as Kissin acknowledges, to separate the contact sites of tobacco products and alcohol; swallowed tars may affect the hypopharynx and the oesophagus. For oesophageal cancer it would be interesting to discover whether or not there are any differences in tumour sites between those who are predominantly smokers and those who are predominantly drinkers: unfortunately, the literature is seldom helpful in this respect. Wynder and Bross (op cit) comment on the fact that early papers often treat cancers of the larynx, pharynx and oesophagus

as though their aetiologies were identical, frequently combining data on three types of cancer to produce one set of rates. Even now, when cancer of the oesophagus is recognised as having aetiological features different from those of cancers of the larynx or pharynx, it is still the exception rather than the rule to include details of tumour distribution within the oesophagus. Where details of tumour sites are known, it might seem useful to classify the studies according to whether they originate in alcohol or non-alcohol cultures, and in so doing acquire some information on tumour sites in tobacco-only populations. Unfortunately, matters are not so simple: leaving aside malnutrition and its important consequences for cancer development, some of the highest-incidence areas also have confounding dietary factors such as the eating of mouldy food or food rich in sharp silica fragments, both of which may mask any effects which might have been detected from tobacco consumption.

Common sense suggests that the effects of alcohol should be felt mainly in the lower third of the oesophagus, where it is held back - if only momentarily - by the lower oesophageal sphincter (LES). The LES is considered an important defence against gastric reflux of hydrochloric acid, pepsin and bile into the oesophagus. Alcohol has been shown to reduce the efficiency of the LES in protecting against gastric reflux and to impair the peristaltic removal of stomach acids once in the oesophagus (Lieber, review paper, 1982), thereby compounding twice over their damaging

effects. Swallowed tars from smoked or chewed tobacco, on the other hand, should have their greatest effect on the upper third of the oesophagus. When the literature is examined, however, it appears that the middle third, where the oesophagus narrows at the level of the left bronchus, is overwhelmingly the site of most tumours. Giarelli et al (1982) summarise the results of nine surveys in which the proportion of tumours at each site is mentioned, to which may be added their (Giarelli et al) own results and those of Mahboubi and Aramesh (1980). In six of the studies (all 'drinking' populations), the proportion of tumours is approximately: upper third, 15-20%; middle third, 55-60%; lower third, 20-30%. Only in Coetzee (1966, S.Africa) and Sadeghi (1977, S. Iran) is the proportion of tumours in the upper third as high as 30-35%. In Mahboubi and Aramesh (op cit), the most common site is the lower third - 60%. Giarelli points out that there may be discrepancies in reporting lower oesophageal tumours, in that they may be wrongly described as cancers of the gastric cardia: correct attribution in all cases would result in the proportion of lower third cases being higher - but by how much it is not possible to say.

4.2.1 Possible mechanisms

From an epidemiological point of view it is perhaps not as important to understand the precise mechanics of tobacco-induced harm as it is, for example, to understand how diet and alcohol

may affect the cancer process. Tobacco confers no positive health benefit whatever (whereas moderate drinking may) and is an avoidable risk; for this reason the account of possible mechanisms is kept to a minimum. Most of the following material is taken from two papers, Wynder et al (1975) and McCoy et al (1980); for the sake of brevity these are simply referred to as 'Wynder' or 'McCoy'.

Among the tumorigenic components of tobacco smoke are polynuclear aromatic hydrocarbons and cyclic nitrosamines (tumour initiators), phenols (tumour promoters), chlorostilbenes and catechols (tumour accelerators). Wynder proposes that alcohol affects the activity of oxidase and dehydrogenase enzymes operating within cell microsomes; in particular, the ability of the enzymes to metabolise polycyclic hydrocarbons is impaired. Although alcohol could - and probably does - act mechanically as a solvent and carrier of tobacco carcinogens across cell membranes, Wynder hypothesises that the real effect of alcohol is to permit tobacco carcinogens to operate by impairing the respiratory enzymes which would otherwise eliminate them. Wynder quotes animal studies in support of his thesis, in particular one by Kuratsune (1971), in which benzo (a) pyrene was given to two groups of rats, one receiving ethanol in drinking water, the other not. The rats receiving ethanol yielded a far greater number of oesophageal tumours than the ethanol-free group.

For a time the polycyclic hydrocarbons were regarded as the principal tobacco carcinogens: recently, however, the cyclic nitrosamines have received more attention. Two important carcinogens, N-nitrosipyrrolidine (NPYR) and N-nitrosornicotine (NNN) have both been detected in tobacco smoke. Of the two, NNN is thought to be the major tumour-producing component of chewed tobacco. NNN induces oesophageal and nasal cavity tumours in rats and a key question even now is whether this unusual organ-specificity in laboratory animals also applies to humans. McCoy hypothesises that both NPYR and NNN may undergo hydroxylation at one of the two alpha-carbon sites, giving rise to unstable intermediates. The final breakdown products are an oxobutylcarbonium ion in the case of NPYR and dinitrophenylhydrazones in the case of NNN. Ames (1983) - quoted in an earlier section - draws attention to the extreme mutagenicity and carcinogenicity of both the hydrazines and carbonium ions. Ethanol has been shown to accelerate the hydroxylation of NPYR and NNN in rat liver cells, extracts from which show enhanced mutagenicity in the Ames test - though the precise mechanisms by which alcohol acts in synergy with these two carcinogens is not at present understood (McCoy).

In the case of the enzyme-impairment model proposed by Wynder, it is possible that alcohol has no direct action on enzyme production but works at a more fundamental level by inducing micronutrient deficiencies. Wynder, citing Walgren (1971),

remarks that alcoholics suffering from vitamin B deficiency have been shown to have reduced respiratory-enzyme efficiency. Since the respiratory enzymes require both riboflavin and iron to function (there is a link here with Plummer-Vinson syndrome), the levels of these two micronutrients will have an important bearing on cell enzyme levels, which in turn may determine whether a carcinogen is activated or inactivated.

4.3.1. Patterns of tobacco consumption in Scotland: the limited evidence

In what is possibly the only study of its kind to include data from Scotland, Cummins et al (1981) studied the drinking and smoking habits of 7735 men aged 40-59 years, chosen at random from the registers of general practices in 24 towns in the UK; the Scottish towns were Ayr, Dunfermline and Falkirk. Most of the results are presented as generalisation from the whole sample; data from the Scottish towns are not analysed or discussed separately in the text but are included in some of the diagrams. The men in the sample were asked to describe their drinking habits according to frequency of drinking and amounts drunk on each occasion. The investigators were especially interested to find out if there were any qualitative differences in the behaviour of daily drinkers and weekend-only drinkers. Smoking activity was categorised as: never smoked, pipe or cigar only, ex-cigarette/now pipe or cigar, ex-cigarette/non smoker now, light smoker (up to 10 cigarettes

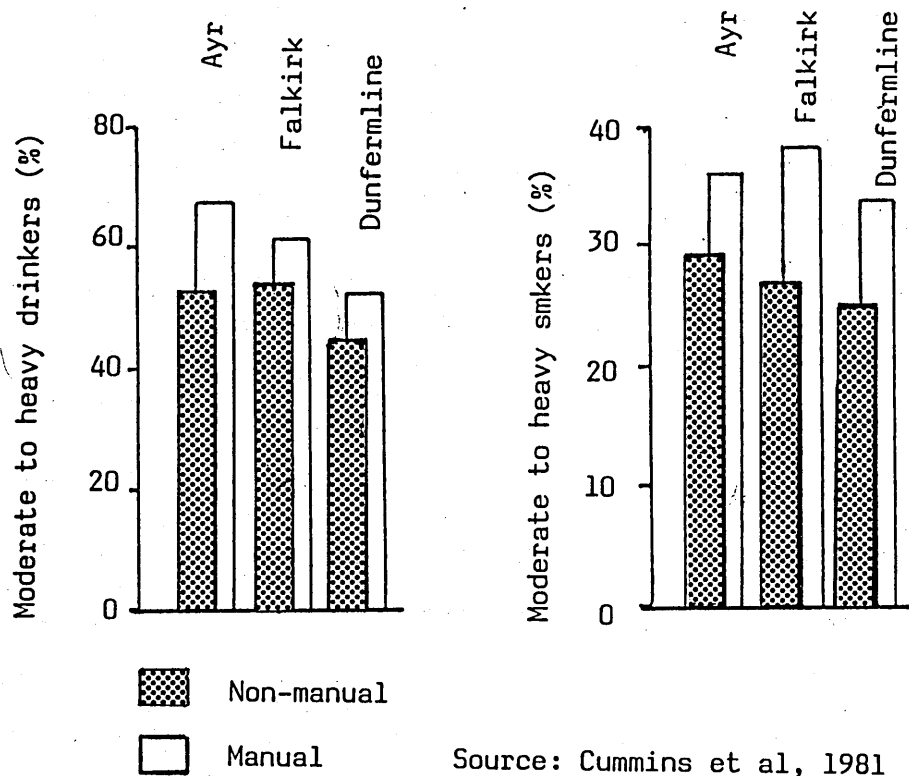
a day or their equivalent), moderate (up to 20), heavy (over 20).

In summary: the survey confirmed the known positive relationship between smoking and drinking. When smoking was used as the independent variable a progressive increase in both habits could be seen, with non-smokers drinking the least and heavy drinkers smoking the most; this was true for both manual and non-manual workers. When drinking was used as the independent variable, the relationship between the two habits was not so straightforward; non-drinkers and occasional light drinkers smoked more than regular light drinkers. This was especially true of non-manual workers. In both sets of data, however, moderate-to-heavy drinking was associated with moderate-to-heavy smoking and vice versa. Cummins et al write: 'Interestingly, the smoking rate of heavy daily drinkers was much greater than that of heavy weekend drinkers, and the positive relationship between smoking and drinking was most pronounced for daily drinkers. These findings suggest that the heavy daily drinkers were different in some way from the heavy weekend drinkers. The possibility of a difference in the underlying reasons for being a daily or a weekend drinker might be worthy of further investigation.'

The data for individual towns gave rise to an unexpected finding. There were, as expected, pronounced differences in smoking and drinking habits between the two social class groupings (i.e. manual and non-manual). However, there were also pronounced

FIGURE 14

Percentage of men classified as moderate to heavy drinkers and smokers by social class in three Scottish towns.



Source: Cummins et al, 1981

differences between individual towns, indicating an effect of location independent of class. Cummins et al did not speculate at any length on why this might be so, but suggested that the different reasons for drinking, e.g. to relieve stress, drinking while dining, as a social lubricant, etc., might correlate with certain characteristics of each town, e.g. dominant industries, proportion of people in work, relative prosperity, etc. Tobacco fulfils similar psychological and social functions for smokers, so it is not surprising that smoking habits also reflect the class and locational variations seen in alcohol consumption. The smoking and drinking patterns found by Cummins et al in the three Scottish towns are shown on the facing page.

Taking averages, there is a clear stepwise progression in drinking behaviour, with Ayr having the highest overall proportion of moderate to heavy male drinkers (roughly 60% of men came into this category), Falkirk in the middle with around 58%, and Dunfermline at the low end with some 48%. Where smoking is concerned, Ayr and Falkirk show similar profiles, each with approximately 36-38% of males smoking more than 20 cigarettes a day; in Dunfermline the figure is around 29-30%. Although the number of towns is too few to perform a valid correlation test, and although none of the male SMRs for oesophageal cancer in the three towns reaches significance, it is at least of interest to note that the descending proportions of heavy drinkers and smokers in each town

is matched by descending SMRs for oesophageal cancer:

TABLE Male SMRs for oesophageal cancer in three Scottish towns

Ayr	149
Falkirk	133
Dunfermline	74

4.4.1 Oral hygiene and edentia

Edentia, which in the West is virtually synonymous with teeth clearance (as opposed to the gradual loss of teeth) has been linked to cancers of the buccal cavity and oesophagus. In the case of the buccal cavity the mechanisms by which dental inadequacy might lead to cancer have been plausibly outlined by Graham et al (1977); the link with cancer of the oesophagus is less obvious.

Graham et al (op cit), looking only at oral cancer, found inadequate dentition twice as common in their cancer patients as among the non-cancer controls. Among men, those who smoked and drank heavily and who had missing or decayed teeth had a risk of oral cancer 7.68 times that for men without those characteristics. Inadequate dentition carried the highest risk ($RR=3.15$ $p<.001$), even when other factors were controlled. Although analysis of dietary habits revealed no important differences between cancer patients and controls, this did not necessarily mean that the nutritional status

of the two groups was identical - the heavy drinkers in the sample may have had alcohol-related nutrient deficiencies. Graham et al suspected that poor dentition preceded the onset of cancer rather than the reverse, and reasoned that the deterioration in dental health could be an aetiological factor in oral cancer. The authors hypothesised a mechanism whereby dental sepsis and/or missing or broken teeth could cause trauma of the periodontia, tongue or other oral tissues, so providing easier entry for chemical or viral pathogens.

Several years earlier, Wynder and Bross (1961) had noted a tendency among their American oesophageal cancer patients to become edentulous somewhat earlier than the control group (patients with cancers at other sites). 13% of the oesophageal cancer patients were edentulous before the age of 50, compared with 5% of controls. Of the non-edentulous, 42% of those with oesophageal cancer had missing or decayed teeth, compared with 21% of the controls. In their Swedish study group, Wynder and Bross (op cit) found that female oesophageal cancer patients had a higher incidence of edentia than male patients: a link was made between edentia in females and the prevalence of Plummer-Vinson syndrome in either its frank or sub-clinical manifestations.

If oesophageal cancer victims as a group become edentulous earlier than other groups, how might the two conditions be related? There is unfortunately no straightforward answer: the reasons for edentia

are very complex and relate to social and educational status, tobacco and alcohol consumption and dietary factors such as the consumption of milk. National or regional customs and attitudes may also play a role: Scottish women are known to ask for or agree to teeth clearance earlier than women in other parts of the UK (Prof.A.Sheiham, Department of Community Dental Health, University College Hospital, London, personal communication, 1984). It is possible that teeth clearance may provide the traumatic stimulus to cancer development in susceptible individuals, though it must be said that the evidence to support such a view is slender (Sheiham, op cit). Nevertheless, trauma, both physical and psychological, does seem to be related to a number of cancers, in ways at present not fully understood, but which may be connected with the immune system¹ (Nature, editorial, 1984).

4.4.2 Edentia in Scotland

Early edentia is one of the components of the 'Plummer-Vinson-like' condition described by Wynder et al (1957) and discussed earlier in this work (section 2.3.5). In the south west of Scotland an anomalously high rate of oesophageal cancer among women suggested the possibility of a Plummer-Vinson-related interpretation: the author accordingly looked for (among other things) literature on patterns of dental health and/or edentia in Scotland. Published information

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1. Immunogenic activity on the part of the oesophageal tumour itself has been postulated by Zhang Yu Hui (1981). The possible existence of an immunogenic, tumour-associated antigen encourages hope that immuno-diagnosis could lead to early warning of the cancer, and immunotherapy to its treatment.

appears limited to works by Todd et al (1974) and Todd and Walker (1980). Todd et al (op cit) looked at tooth loss in a sample of 2290 Scottish men and women (M=1070, F=1220) and found that 44% of adults over the age of 16 had no remaining natural teeth, a higher proportion than in England and Wales (where a 1968 survey had shown that 37% were edentulous). The authors break down tooth loss in the Scottish sample by age, sex and social class and show that the highest levels occur in the semi-skilled and unskilled classes, which were 53% edentulous overall. In contrast, social groups I-III had 33% edentia. At all ages above 16, Scottish women showed higher levels of tooth loss, the difference being most marked in the 35-44 age groups, where the proportion of edentulous females was 65% higher than that for males. Neither Todd et al (1974) nor Todd and Walker (1980) contain any reference to spatial variations in edentia levels within Scotland.

CHAPTER FIVE: SOME GEOCHEMICAL AND BIOLOGICAL CORRELATES OF
GASTRIC AND OESOPHAGEAL CANCER

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CHAPTER FIVE: SOME GEOCHEMICAL AND BIOLOGICAL CORRELATES
OF GASTRIC AND OESOPHAGEAL CANCER

5.1.0 Introduction

In Chapter Two some effects of trace metal deficiency on carcinogenesis were considered. In contrast, sections 5.1.0-5.1.5 (below) deal with the possible carcinogenic consequences of metal excess. The emphasis here is mainly on the spatial distribution of metals in surface deposits and water supplies: links between oesophageal cancer and occupational exposure to metals are explored in Chapter Six. Section 5.2.0 reviews the tenuous links between some alimentary tract cancers and natural radiation.

Many of the works cited below are concerned to establish a possible link between metal excess and gastric cancer: other alimentary tract cancers are mentioned - sometimes incidence figures are included - but their statistical treatment has been at best superficial. The chief problem is one of aggregation, with oesophageal cancer data lost among the combined data for 'other cancers of the digestive tract.' Despite a degree of structural uniformity throughout the alimentary tract (see entry in Gray's Anatomy, 35th Edition, 1973), there are - manifestly - sufficient differences in epithelial cell form and function for particular carcinogens to affect particular organs. In some instances, conditions favouring one type of cancer would seem inimical to the development of cancer at another site: for example, it is obvious from any atlas of cancer mortality

that there is virtually a reciprocal relationship between gastric and colonic cancer. Mesle (1984) describes the maps of stomach and intestinal cancers in Europe as being 'almost perfect negatives' of each other. Clearly, there are definite, though barely understood, processes of organ specificity at work. Why then review literature which largely concerns stomach cancer, when the interest is primarily oesophageal cancer?

One reason is that many of the references to oesophageal cancer and metal excess in the United Kingdom are found in works whose main concern is stomach cancer: necessity, therefore, leads to their use. Also - organ specificity notwithstanding - common links may sometimes be discerned between cancers at different sites. For example, mortality ratios for stomach and oesophageal cancers in North Wales are twice the national average (although the two are seldom exactly co-extensive in distribution), while in Scotland plumbers have a very high mortality ratio for oesophageal cancer. It is tempting to see lead as the common factor: there seems a good spatial correlation between lead and stomach cancer in Wales, and a good occupational correlation between lead and oesophageal cancer in Scotland. Obviously the link is not direct and absolute, or oesophageal cancer and lead would correlate better in North Wales, however, it does seem that a connection at some level between the metal and the two cancers cannot be ruled out.

5.1.1 Heavy metals and cancer

Legon (1951) noted that Welsh areas with low mortality rates for gastric cancer were associated with good drainage and an absence of peaty soils, whereas high mortality areas were characterised by poorly-drained, peaty soils. Legon surmised that peaty soils gave rise to deficiency diseases of crops which, in turn, affected domestic animals and people. Soil mineral deficiencies, in particular the association of zinc and molybdenum deficiencies with crop nitrate/nitrite levels and cancer, were discussed in Chapter Two. Insofar as metals may be implicated at all in oncogenesis, it would appear that environmental excess of certain metals, rather than any deficiency, correlates better with observed patterns of cancer distribution in the United Kingdom. Legon may still be correct, however, in identifying acid soils as an important factor in the metal/cancer association.

In Britain the ancient upland areas of igneous and metamorphic rocks are rich in non-ferrous metals and also account for some of the largest expanses of acid, peaty soils. It is known that acid soils mobilise heavy metals (J. Pitman, Department of Geography, University of London, Kings College, personal communication, 1984) and that in such areas, metals are leached from the rocks to appear lower down in alluvial deposits and living organisms. Metals also get into the environment by other routes. Ore deposits give rise to extractive and processing industries which, in the past, have

resulted in emissions of material to surrounding land, water-courses and the atmosphere. In their studies of gastrointestinal cancers in North Wales, Stocks and Davies (1960 and 1961) found extremely strong correlations between high rates for a variety of cancers and heavy concentrations of certain metals. They were unable to explain, however, why soil-metal concentrations varied widely within small areas, and why dietary samples often did not reveal the expected high levels of metals. (They surmised that toxic metals got into the system by direct contact/ingestion, e.g. from gardeners' hands.)

With the publication of the Wolfson Geochemical Atlas of England and Wales (Webb et al, 1978) giving for the first time accurate, countrywide information on surface trace metals, and the recent publication of the Atlas of Cancer Mortality in England and Wales (Gardner et al, 1983), it is now possible to see how close is the correspondence between some of the older metal-extracting areas and some of the local authority areas with elevated rates for gastrointestinal cancers. There are, however, many anomalies when it comes to matching high cancer rates with high metal concentrations. Not all metal-rich areas have high cancer rates and some areas with high cancer rates are not associated with metal concentrations (at least, not as found in surface deposits). There is also the problem of metal uptake by plants and the subsequent ingestion of the plants by animals and humans. Some metals are

not taken up by plants even when present in large amounts in the soil, so that soil levels are not necessarily an indicator of excessive levels in plants, animals or humans. On the other hand, contaminated soil can be ingested directly by animals, leading to raised tissue levels of some undesirable metals. Field and Purvis (1964) showed that during winter months, when grass may be pulled out of the ground with roots and soil, ingested soil could amount to as much as 14% by weight of the sheep's food intake (expressed as dry matter equivalent). Thornton (1974) found that cattle in south west England were eating 140-1400g soil/day during winter months and that soil ingestion accounted for 1-10% of dry matter intake. Healy (1968) suggested that ingested soil was an important source of trace elements in sheep and cattle. However, undesirable elements may also be picked up and passed on to man. Kovalsky and Yarovaya (1966) report that bovine molybdenosis in a molybdenum-rich area of Armenia is associated with a 30% incidence of endemic gout in humans.

5.1.2 Toxic/heavy metals in the marine environment

Waste waters from cities and jettisoned industrial wastes are the main sources of toxic and heavy metals in sea water. In the USA Bradford (1971) found that the highest concentrations of copper, lead and zinc derived, as one might expect, from urban waste waters. Cadmium, chromium, molybdenum and vanadium came almost entirely from miscellaneous industrial wastes. Environmental mercury

derives principally from agricultural seed dressing, but this is less likely to create problems than dumped industrial wastes (a process stringently controlled in the United Kingdom under the terms of the Oslo Convention). In general, mercury is held tightly in the top two inches of soil: even when it eventually leaches out and reaches the sea there is a strong tendency for Hg to sink rapidly and combine with sulphides in anaerobic sediments (US Government Printing Office 1976). In the United Kingdom, concentrations of trace metals in river waters have been exhaustively analysed and their effects reviewed by the Water Research Centre, Medmenham, Bucks, and summarised in Wilson (1976).

5.1.3 Metals in marine animals

The ability of fish and shellfish to act as 'sinks' for toxic metals, pathogenic organisms and radioactive materials has long been known and is extensively documented. In the United Kingdom the Ministry of Agriculture, Fisheries and Food has produced a series of comprehensive reviews on pollutants in marine organisms: those relevant to this study include copper and zinc (MAFF, 1982) and cadmium (MAFF, 1983). Radioactive discharges to the marine environment are discussed by Leonard et al (1982).

Concentration factors for injurious substances in marine organisms may reach five orders of magnitude and some of the most commonly occurring substances may be significant for some types of carcino-

genesis. Maximum concentration factors for radionuclides reported by Polikarpov (1967) include:

Radionuclide	Maximum reported concentration factor
chromium ⁵¹	10^4
cobalt ⁶⁰	10^4
copper ⁶⁴	5×10^3
zinc ⁶⁵	5×10^3

Under exceptional conditions, however, concentration factors can far exceed even the high rates shown above: Perkins et al (1960) report an accumulation of zinc⁶⁵ in oysters corresponding to a concentration factor 200,000 times that of the surrounding seawater.

Heavy concentrations of stable elements corresponding to the above radionuclides have all been detected in fish and shellfish (MAFF reports, cited above). The specific role, if any, of toxic/heavy metals in oesophageal carcinogenesis is not known, but it should be mentioned that such substances may be present in the diets of people living along certain stretches of the coast of Britain. The fact that fish and shellfish are landed at coastal towns does not necessarily mean that they are eaten on the coast in greater amounts than inland - though common sense suggests that fishermen will avail themselves of at least some of their catch. Even if consumption were found to be higher in coastal towns, it still does not follow that the permanent residents are consuming the

excess fish and shellfish. It could be, for example, that holiday visitors or day trippers were responsible. However, unpublished National Food Survey data suggest that families resident on the coast do in fact eat more fish and shellfish than families living inland (D. Buss, Head of Nutrition Section, Min.Ag.Fish. & Food, personal communication, 1984). Studies of particular communities have shown that people eating fish and shellfish from their localities are exposed to increased health risks (Hunt et al, 1982). The necessary matching of food survey data with mortality data and biopsy/autopsy investigations has not been done, so that it is not possible to say with confidence that groups who ingest certain metals are definitely at higher risk of developing alimentary tract cancers. However, plausible mechanisms exist and the subject would repay investigation. Many factors are involved and it is appropriate to draw attention to the closely interlinked nature of some of the variables.

For example: Coastal dwellers tend to eat more fish and shellfish than people inland, and fishermen almost certainly eat a fair amount of their catch. Both groups, therefore, are probably exposed to higher intakes of heavy metals (and perhaps their radionuclides) than other groups. Fishermen are a notoriously high-risk group for alcohol-related problems. Chronic drinkers may suffer a number of dietary and metabolic nutrient deficiencies, in the presence of which the toxic (and possibly carcinogenic) properties of some

metals are enhanced. Even without the alcohol factor some metals are antagonists for important trace elements in the body (e.g. cadmium removes selenium; discussed below). By displacing vital elements in the body the usurping metal not only exerts its own toxic or carcinogenic effect, it also impairs the immune defences of the body to just such an attack. Sections 5.1.4-5.1.8 following review the evidence relating to eight metals.

5.1.4 Lead

A recent United Kingdom report on lead in food found no clear evidence of carcinogenicity (MAFF, 1982). Although rats develop renal tumours in response to inorganic lead salts the MAFF report observes that this only happens at levels which would be lethally toxic to humans: the conclusion, therefore, was that any carcinogenic risk from lead would be very small. Yet doubts persist.

Reports linking lead with a range of cancers go back many years. Young and Russell (1926) (quoted in Oettlé, 1967) found a high risk of oesophageal cancer among metal workers, particularly those exposed to lead, bronze and brass. The extraordinary rise in oesophageal cancer in parts of South Africa during the 1950s and 1960s led Oettlé (among others) to look for evidence of an 'intrusive carcinogen' during the previous 15-20 year latency period. Oettlé (1961, 1964 and 1967) identified the plating on oil drums as a possible culprit. From 1941-49 a shortage of tin in South

Africa led to kerosene drums being plated with a mixture of tin and lead, known as 'terne plate' (Fr: terne = dull, tarnished), instead of with pure tin. Such oil drums were used for the brewing and distilling of local alcoholic beverages, and these beverages frequently digest their metal vessels and contain lead and other trace metals (Oettle, 1967). The use of terne plate declined rapidly after 1949 and vessels plated by this process would have disappeared from use in the succeeding years. Warwick and Harington (1970) observe that, if the terne plate hypothesis is correct, the decline in use of terne-plated vessels during the late 1950s should be reflected in falling rates for oesophageal cancer some time during the 1970s. However, a recent report on smoking and drinking in the Transkei (Bradshaw et al, 1983) not only fails to mention any decline in mortality rates, it also omits any mention of minerals in alcoholic beverages, as if - without actually saying so - the idea had been dropped.

An earlier paper by Bradshaw and Schonland (1969) had reported an excess of oesophageal and lung cancer among the Xhosa, almost all of whom smoke pipes (women as well as men) and whose pipes were frequently lined with lead. No mention of the latter fact was made in the later paper by Bradshaw et al (1983). However, Bradshaw and Schonland (op cit) also found that the oesophageal cancer group had an excess of workers who may have been exposed to lead at work, e.g. plumbers, painters, battery makers, printers and welders.

Stocks and Davies (1960) found a moderately strong correlation between soil lead levels and intestinal cancer in North Wales and Cheshire, but got an inconclusive result in Devonshire. In North Wales and Cheshire, levels of soil lead in the gardens of 'non-cancer houses' were lower than in the gardens of houses where people had died of intestinal and oesophageal cancer. The percentage of gardens with lead levels over 5.00ppm was 44% among non-cancer households and 59.2% for cancer households, a difference of 15.2%.

The Wolfson Geochemical Atlas (op cit) shows lead levels to be very high (as much as 320ppm) in parts of North Wales, the chief surface deposits being found in the vicinity of Ffestiniog, Conway, Colwyn Bay, St. Asaph and rural Flint. A comparison of the same areas in the cancer atlas of Gardner et al (op cit) shows every one to have significantly high oesophageal cancer rates for one or other sex (though only rural Flint has high rates for both sexes). In the much earlier study by Legon (1952) gastric cancer mortality was found to be elevated in the districts of Hiraethog and Penllyn, also areas with fairly high levels (80-160ppm) of surface lead. Further south, Machynlleth borders a high-lead area and also has a moderately high oesophageal cancer rate for women, but low rates for men. Rural Brecon and Abergavenny both show raised lead levels in the Wolfson atlas: both also have raised oesophageal cancer rates (moderately high for men in Abergavenny, high for women in Brecon). Although the spatial concordance between lead and cancer areas in Wales is striking, two cautionary points

should be made: not every high-lead area has high rates for cancer (Derbyshire and Cumbrian lead-mining areas, for example), and lead seldom if ever occurs in isolation: many of the lead areas in the Wolfson atlas also coincide with areas high in zinc, copper, cadmium, barium, manganese and molybdenum.

In the USA Berg and Burbank (1972) found that metal concentrations in water supplies not only correlated well with areal cancer mortality statistics, but that particular metals produced tumours in laboratory animals at sites closely corresponding to human tumour sites for the same metals: in their study lead was associated with leukaemia, bowel and kidney cancer.

If lead does enhance the risk of oesophageal cancer it is more than probable that the link is indirect and that other factors are also involved. In the rat, iron or chromium deficiency increases the toxicity of lead (Six and Goyer, 1972), and it might be that lead also increases the risk of cancer in iron-deficient individuals. Certainly in parts of North Wales - where cancer rates and lead levels are high - there are known to be higher than average rates of the iron-related Plummer-Vinson syndrome among women (maps in Gardner et al (op cit) suggest that oesophageal cancer is slightly more widespread among women than men in North Wales). Iron deficiency is also common among alcoholics, whose distribution is greater among the lower socio-economic classes and who are more likely, therefore, to live in older, poorly maintained

properties, many of which may have lead piping.

Oesophageal cancer and occupational exposure to lead in Scotland

Oesophageal cancer mortality in lead-related occupations is well above average, corroborating to some extent the earlier findings of Young and Russell (op cit) and Bradshaw and Schonland (op cit). However, it is difficult to assess the true strength of the relationship because of problems with the Scottish data. In data supplied to the author², the age-specific populations of occupation units 045 (plumbers, lead burners and gas fitters) and 046 (pipe fitters and heating engineers) were aggregated at source: disaggregated data are not available. While it is likely that workers in all the above categories are exposed to lead in varying degrees, those most exposed are likely to be plumbers and lead burners. Mortality in the combined occupations is analysed in Chapter Six: briefly, however, there were no deaths in 1970-74 among pipe fitters and heating engineers (unit 046), whereas there were 11 male deaths in those occupations which had an overt connection with lead (plumbers and lead burners, etc - unit 045). The SMR for the two occupation units (males) was 156, but with the combined populations the result was not statistically significant. Without the diluting effect of the men in unit 046 the SMR for men in unit 045 would obviously have been higher, but by how much and whether significant is is not possible to say from the available data.

2. The scope and format of the data are described in Chapter Six, section 6.2.0.

5.1.5 Cadmium and zinc

Cadmium and zinc are closely associated in nature: cadmium is the principal contaminant of zinc ore and, conversely, zinc deposits are the main source of cadmium. In the United Kingdom, zinc-cadmium deposits are or were mined at Bishopton in Strathclyde (Read, 1956).

Zinc is essential to life but has been reported as toxic in large amounts: however, it may be that the apparent toxicity of zinc is due to the presence of small amounts of cadmium (Schroeder, 1967). McGlashan, (1967 and 1969) mapped the incidence of oesophageal cancer in central Africa and found the area of highest incidence - Malawi and part of eastern Zambia - to be exactly co-extensive with the drinking of 'kachasu' or Malawi gin. On analysis, the chief ingredient of kachasu - maize beer - and the final distillate were found to have extremely high levels of zinc, up to 25mg/l and 31mg/l for the beer and spirit respectively. This, as McGlashan points out, far exceeds the safe limit of 5mg/l drinking water laid down by the WHO. Comparison of spirit preferences among oesophageal cancer patients yielded a strong positive correlation between the cancer and the kachasu drinking ($p < .001$), with drinkers of other types of spirits accounting for less than 20% of oesophageal cancer patients in high-reporting hospital areas. McGlashan, quoting Upadhyay (1967), notes that the zinc from vessels used in preparing kachasu may be dissolved by acids, absorbed by yeasts and

distilled over at relatively low temperatures in a metallo-organic form. Pace Oettlé (1961, 1964, 1967) no traces of iron, lead or tin were found in kachasu. If zinc excess is relevant to carcinogenesis, then a mechanism has yet to be found: unless of course it is not the zinc at all, but a contaminant such as cadmium.

Shakman (1974) refers to cadmium as '...a poison without redeeming features': even small amounts are toxic by ingestion and inhalation. It damages the kidneys and gastrointestinal tract in mammals and also produces anaemia. Ames (1983) states that the cation of cadmium (Cd^{2+}) is also a known carcinogen. Cadmium is a selenium antagonist and Ames offers an explanation of how this aspect of the element might play a role in tumour initiation. To summarise: Glutathione peroxidase is an essential enzyme in the destruction of lipid hydroperoxides and endogenous hydrogen peroxides. It thus helps prevent lipid peroxidation and damage to DNA (see also section 2.1.5 final paragraph). Glutathione peroxidase is an important antimutagen, while the transferases are major defences against oxydative and alkylating carcinogens. Selenium is the active site of glutathione and cations of cadmium (and mercury) lower the activity of the enzyme by interacting with selenium. Cadmium also competes with zinc for thiol-group binding sites on the protein metallo-thionein (Shakman, 1974 - quoting Jacobs et al, 1969). Cadmium thus has a dual effect in that, as well as its own toxic and carcinogenic properties, it also lowers

body zinc levels which may, in turn, impair body defences against carcinogenic attack.

Berg and Burbank (1972) sampled populations in 16 major water basins of the United States and found an extraordinarily high correlation between cancer of the oesophagus and waterborne cadmium ($p = .00004$) and very strong correlations between cadmium and cancers of the lung ($p = .001$), mouth ($p = .003$), larynx ($p = .004$) and Bladder ($p = .009$). The authors are rightly cautious, however, about accepting these findings at their face value. Cadmium distribution in the USA exhibits a particularly orderly gradient (low in the south-west, high in the north-east) and any other factor with the same distribution would show a good correlation, even if there were no real connection. It happens that the two regions with the highest waterborne Cd levels are also the regions with the heaviest consumption of tobacco and the highest rates for smokers' cancers. It also happens that Cd is present in tobacco smoke, so that there is bound to be a positive correlation between body cadmium levels and smokers' cancers, regardless of whether there is any causal connection.

Cadmium is used in certain industrial processes (e.g. electroplating and the manufacture of electrical transmission wires and some pigments) and some may escape into the environment as waste products from these sources. Cd also occurs as a minor contaminant of certain plant foods, notably cereals (Shakman, 1974), and a major contaminant of shellfish. Brown meat from crabs taken in British waters has been found to contain Cd in concentrations ranging from 0.2 - 86mg/kg (MAFF, 1983). People eating fish and

shellfish are exposed to significantly higher levels of cadmium than those who do not eat these items: the mean weekly intake of people eating fish and shellfish has been measured at 40µg/person, compared with less than 3µg/person for those not eating fish and shellfish (MAFF, 1983). Cadmium intakes among people living along British shores have been measured at selected sites: groups in SW Cumbria, Looe and Plymouth had the highest mean weekly intakes at 117, 218 and 344µg/person respectively (MAFF, 1983). Of these three places only Plymouth has significantly high oesophageal cancer ratios in both sexes (see Gardner et al, 1983), and only Plymouth is also associated with locally high surface concentrations of cadmium (see Webb et al, 1978). However, Plymouth is a port and this fact alone may have more bearing on oesophageal cancer than cadmium levels (see section 6.3.3.).

Cadmium has been directly implicated in human carcinogenesis only in the case of cancer of the prostate (Berg, 1975; Higginson, 1975) but the numbers have been small and a causal link not absolutely certain. Although specific links with other cancers are unproven, cadmium must nevertheless remain suspect: it is a known teratogen (Beliles, 1975) and mutagen (Ames, 1983) and, perhaps most significantly, is intimately associated in both its occurrence and metabolic effects with zinc. Bearing in mind that cadmium is almost universally a contaminant of zinc, and that where high zinc levels exist there are likely to be proportionally high levels of cadmium, it is worth quoting at some length from Stocks & Davies (1961):

'In North Wales the stomach cancer soils show a wide range of [soil-zinc] values from 4 to 441 parts per million, with a mean of 81.2ppm compared with 51.2ppm for the non-cancer controls, the excess of 30.0ppm being twice its standard error. In Cheshire the stomach cancer soils show a range of 3 to 387ppm, with a mean of 83.4ppm compared with 54.3ppm for the controls, the excess being 1.5 times its standard error.

'In the two Devon localities where the zinc levels happen to be higher, the mean for the stomach cancer soils is 181ppm compared with 103ppm for the matched controls, giving an excess 2.8 times its standard error.

'The odds against finding such agreement in three independent series by chance, with $t=20$, 1.5 and 2.8, are enormously great and it must be concluded that a zinc content of the soil higher than the local average is a factor favourable to the appearance of stomach cancer, and that this is not confined to districts where the general incidence is very high.'

Against the above, however, is the case of Shipham in Somerset, an old zinc mining village. Residents of Shipham ate vegetables grown in soils with high levels of zinc and cadmium, but a survey of mortality data covering a forty year period did not show any excess cancer mortality in the village. (Inskip et al, 1982).

Finally, the absorption of cadmium is significantly increased at low serum iron levels (Flanagan et al, 1978 - quoted in Lieber et al, 1979). Depressed iron levels are common in women of child-bearing age and in alcoholics (see also section 2.3.3); the cancer risks of the latter group have been mentioned several times in these pages.

5.1.6 Chromium

Chromium exists in 2-, 3- and 6- valent forms. Bivalent chromous salts are probably too uncommon to concern us here. Trivalent chromium is not toxic, indeed small amounts (around 0.15mg/day for a 'reference man') are necessary in glucose metabolism (MAFF, 1976). Hexavalent chromium is markedly toxic, produces haemorrhages of the gastrointestinal tract³ when ingested, and may be implicated in cancers of the respiratory tract (Samitz, 1970; Carter and Symington, 1975). As a pollutant, high levels of chromium are found in the air of heavily industrialised areas and as a minor contaminant of water supplies. Tobacco smoke provides abundant chromium (Shakman, 1974). Stocks and Davies (1960) found that soil chromium levels were consistently higher in gardens of houses where cancer

-
3. It is interesting that a number of suspect gastrointestinal carcinogens should produce anaemia, haemorrhages or both. These effects were found associated with bracken in Chapter Two, and here in connection with Cd and Cr. The author wonders if anaemia with haemorrhagic conditions of the gastrointestinal tract are in any way predictive of gastrointestinal cancer, whatever the precipitating factors, or, as a corollary, whether any substances which produce the two conditions should be regarded as potentially carcinogenic?

deaths (including oesophageal cancer) had occurred, than in gardens of houses where non-cancer deaths had occurred. At soil concentrations of 0.3-0.6ppm (giving a mean value 0.065ppm above the mean in control areas) there was a strong correlation ($p < .001$) with stomach and other alimentary tract cancers.

Nicholson (1960) found locally high stomach cancer rates in a Devon township: rates in the surrounding areas were average. There was a significantly high excess of chromium, zinc and cobalt in the garden soils of houses where cancer deaths had occurred: these same houses were also within two sub-districts, each of which had a tannery. Both tanneries used chromium and the deaths occurred among those who might have been expected to have eaten much of their own garden produce.

Against the above, Berg and Burbank (1972) failed to find a statistically significant correlation between any form of cancer and chromium ingested via water supplies. A convincing role for chromium in cancers of the alimentary tract has yet to be established. However, the fact that chromium is known to damage the intestinal mucosa and was one of a group of metals strongly associated with gastrointestinal cancers in North Wales, suggests that a causal connection should not be ruled out.

5.1.7 Cobalt

In each of the areas investigated by Stocks and Davies (1960), soil-cobalt levels were higher in the stomach cancer series than in the non-cancer series, the excess of cancers in each instance being more than twice their standard errors. The authors regard the odds against such a result arising by chance as very great and conclude that a high cobalt level in the soil is conducive to the development of stomach cancer. There were no significant differences however, between soil-cobalt levels in the 'other cancers' series (which included oesophageal cancer) and those in the non-cancer series.

There is an excellent visual fit between surface cobalt levels (Wolfson) and the stomach cancer ratios given in Legon (1951), with a clear north-south gradient in both. In the northern part of Anglesey cobalt levels are around 20ppm and the male stomach cancer SMR is 145. In the southern part of Penllyn RD cobalt levels are 80ppm and the male SC ratio is 175. In contrast, the fit between soil cobalt levels and oesophageal cancer ratios is poor, with high but not significant cancer ratios in one rural area only (Penllyn). All of which lends support to the views of Stocks and Davies, that cobalt is perhaps connected with stomach cancer in some way, but only slightly - if at all - with other forms of alimentary tract cancer. Berg and Burbank (1972) found no correlation between cancer and cobalt levels in US water supplies.

5.1.8 Copper and iron

Stocks and Davies (1960) found the mean copper content of soils in their three cancer areas to be slightly higher than the control mean, but no convincing evidence was found to support a view that copper might be implicated in stomach or other gastrointestinal cancers.

In Devonshire and North Wales the soils of the stomach cancer series were found by Stocks and Davies (1960) not to differ significantly in iron content from those in the non-cancer series, the mean level, if anything, being below expectation. Nor were any appreciable differences found in soil iron levels between 'other cancers' and the control series. The finding that North Wales had soil iron levels below expectation accords, superficially, with the above average incidence of Plummer-Vinson syndrome among women in this area. In reality, the association is unlikely to mean anything: Millar (1961 - quoting Howe, 1959) states that, with the exception of potatoes, 78-85% of vegetables are imported into North Wales.

5.2.0 Natural radiation

Traces of uranium and thorium are found in rocks at many sites in Britain. Naturally high background radiation levels are a feature of Aberdeen granites, the Upper Cambrian and Silurian shales of North Wales and mineral veins in Cornwall. Uranium ores have been

sporadically mined in Cornwall (Read, 1959) and substantial untapped deposits exist north of Stromness in Orkney.

The initial decay product of uranium is the gas radon²²² and there is a large literature both on the mechanisms by which radon becomes trapped in buildings made of or situated on granite, and on the possible biological effects of radon concentrations (reviewed in O'Riordan et al, 1983). The principal concern with background radiation is the possibility of excess cancers of a diffuse nature, such as leukaemias, or of lung cancer from inhaled radon. However, there are also some pointers, admittedly tenuous, to the involvement of radioactive decay products in gastrointestinal tumours: for this reason the rather sketchy evidence is reviewed here.

Knowledge that high levels of background radiation and gastric cancer co-exist in parts of Wales led Stocks and Davies (1960a) and Millar (1961) to investigate the possibility of a causal connection. Millar (op cit) analysed rock and water samples in Montgomeryshire for uranium but found only minute amounts. Even in the high cancer localities uranium levels in drinking water did not exceed 2×10^{-6} g/l, nor did radiation levels exceed 0.6 μ C/l. Millar remarks that '...serious significance can hardly be attached to such extremely small amounts of radiation.' Of more consequence, Millar believes, are the further decay products of uranium. Radon²²² escapes into the atmosphere and within about

two weeks had decayed through four radionucleides into lead²¹⁰. Lead²¹⁰ is particulate and falls to the ground in rain, deposition being greatest in areas with heavy rainfall. Lead²¹⁰ decays to polonium²¹⁰, which has a half-life of 138.7 days and is an alpha emitter. Alpha particles (= the helium nucleus) are characterised as 'hard radiation' and, although their penetrating power is slight, (one or two millimetres in human tissue) their energy exchange is such that they can be very damaging. Alpha emitters, even those with short half-lives, are potentially dangerous if inhaled or ingested.

Mayneord et al (1960) found that polonium²¹⁰ forms about 84% of the total natural radioactivity in pasture plants. Strontium⁹⁰ (a beta emitter), lead²¹⁰ and polonium²¹⁰ are trapped in the slow-growing matted grass pastures typical of the peaty, acid soils of the Welsh and Scottish uplands. Mayneord et al (op cit) found that soil alpha activity was 15 times higher in Welsh upland areas than in the drier, basic soils of south east England. In areas remote from large towns meat consumed is often locally produced and slaughtered: in Wales this means sheep and cattle which have grazed upland pastures (Millar, op cit). Millar considers that polonium²¹⁰ may gain access to the human body disproportionately through beef and mutton in Welsh districts and, moreover, that '...the radioactivity of polonium²¹⁰ might be expected to enhance or exceed the effect of any toxicity inherent in the [stable]

element itself.' The latter observation may be important. If the action of certain elements in the body is organ-specific - either because the elements themselves are organotropic, or because particular organs are involved in their metabolism and elimination - then it is entirely plausible that radionuclides of the same elements should have considerable carcinogenic potential at the target sites. An obvious example - though perhaps something of a special case - is the specificity and carcinogenicity of iodine¹³¹ for the thyroid. Another point to bear in mind is that polonium belongs to the same periodic group as sulphur and selenium, elements which have profoundly important biological functions. The author has not been able to explore the possibility that polonium may be able to substitute for either of these elements, but raises the matter in passing.

Fink (1950) investigated tissue polonium levels in domestic food animals and found, as expected, high concentrations in the liver and kidneys: he did not, however, find evidence of polonium build-up in gastric tissues. Nevertheless, some evidence for a gastrointestinal effect of radiation comes from Sweden. Millar (op cit) states that there are shales in Sweden with levels of radioactivity several times that of the Welsh shales. He (Millar) also states, though without giving numerical information for specific localities, that these same shale areas have a high gastric cancer mortality and make a major contribution to the overall high rates for this

cancer in Sweden, compared with England and Wales.

It happens that some of the highest oesophageal cancer rates in mid- and northern Wales are found in areas situated on radioactive shales. In the otherwise moderate-incidence area of Montgomery (now in Powys) Millar (op cit) found death rates of 28.8/100 000 males in Forden Rural District and 23.7/100 000 females in Llanfyllin Borough. In Cornwall the high-significance oesophageal cancer area around Padstow and Wadebridge (see Gardner et al, 1983) also coincides with an area locally rich in uranium minerals. However, it is probably unwise to read too much into these associations. In Scotland the principal areas of radioactive rock (Aberdeen and the Orkneys) show rather low oesophageal cancer rates, while in Cornwall the dense network of lead, zinc and tin workings in the Padstow area would seem to offer a more promising subject for investigation.

5.3.0 Conclusions

There is a large literature on metals and cancer but no incontestable evidence linking any one metal with cancer of the oesophagus. However, plausible mechanisms exist by which metals might affect tumour development and there remains too much circumstantial evidence of a metal/oesophageal cancer connection for the subject to be altogether dismissed.

Of all the metals considered above, lead appears the best candidate for further investigation. Although rejected as a cancer risk in a

recent government report (cited above), there is nonetheless a thread running through the literature associating oesophageal cancer with occupations involving lead. This association was also found in the present study (see Chapter 6), albeit the number of deaths was small and the sample diluted with workers not primarily engaged in working with lead.

From the author's reading of the literature it seems that much epidemiological work on metals and cancer predates advances in understanding how yeasts, bacteria and certain marine organisms can synthesise metallo-organic compounds with very different properties to the inorganic salts of the same metals. It seems probable that retrospective and prospective studies of groups involved in harvesting, processing and selling shellfish might yet throw light on a metal/oesophageal cancer relationship, particularly if the statistical work were complemented by clinical studies of tissues and metal-dependent enzyme systems (autopsy testing for inorganic salts is generally of little use (Mills, 1974)).

PART TWO

**OESOPHAGEAL CANCER IN SCOTLAND: SPATIAL AND
OCCUPATIONAL MORTALITY IN THE YEARS 1970-1974**

CHAPTER SIX: CHARACTERISTICS OF THE STUDY POPULATION

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- 6.0.0 Prefatory note.
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 - 6.1.1 Overall mortality experience: Scotland compared with England and Wales.
- 6.2.0 Description of the study population: number of deaths, crude death rates, age-specific death rates, median age at death.
- 6.3.0 Oesophageal cancer and occupation in Scotland: distribution of deaths by occupation order and crude death rates.
 - 6.3.1 Oesophageal cancer and occupation in Scotland: selection of occupation units for analysis, preliminary remarks and selection criteria.
 - 6.3.2 Further limitations of the data:
 - 1) The 10% Economic Activity Sample.
 - 2) Occupational descriptions on death certificates.
 - 6.3.3 Analysis and discussion of oesophageal cancer mortality in selected occupation units:
 - 1) Occupations with high SMRs.
 - 2) Occupations with low SMRs.
- 6.4.0 Brief summary.

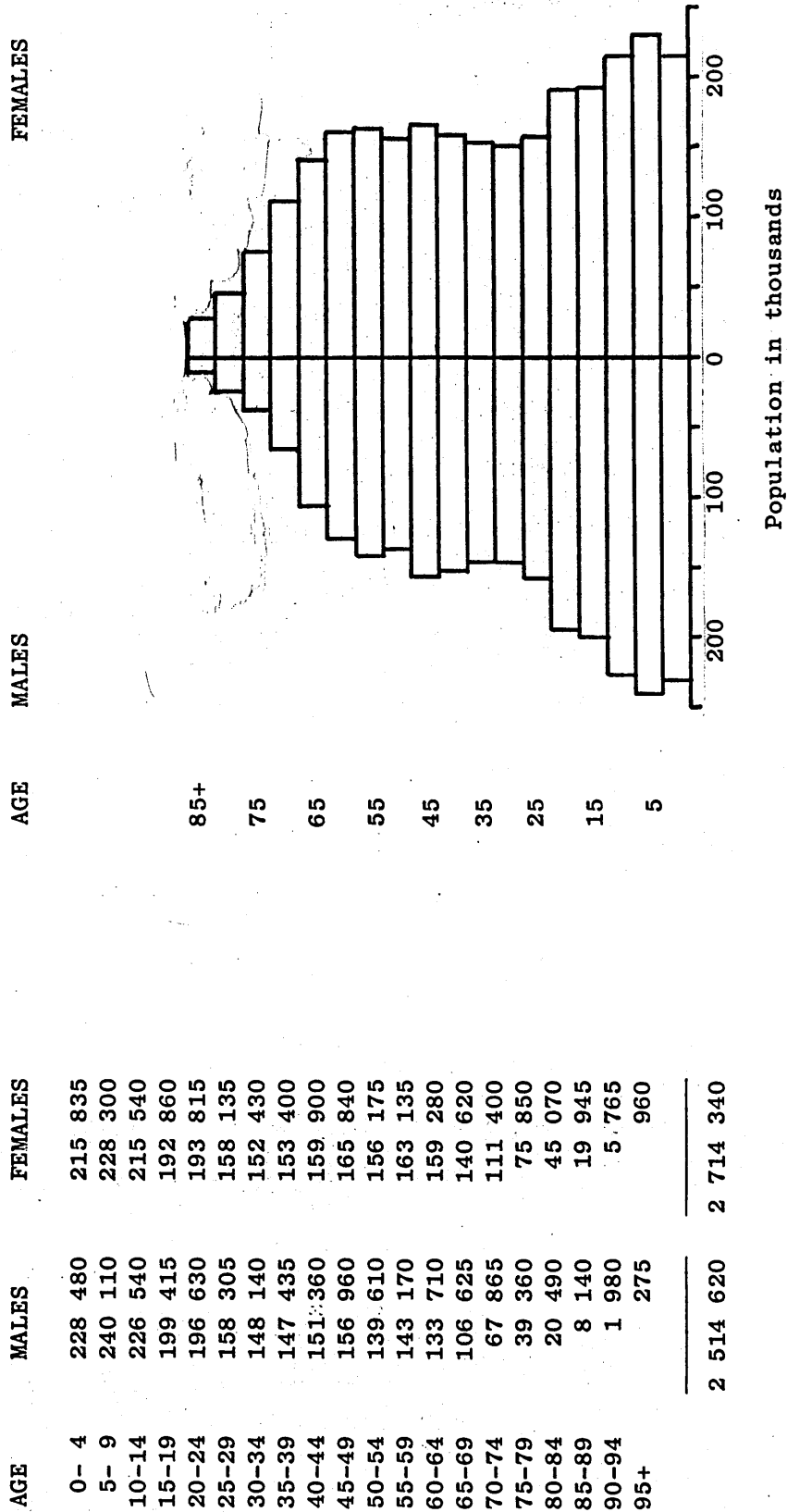
CHAPTER SIX: OESOPHAGEAL CANCER IN SCOTLAND 1970-74:

THE STUDY POPULATION

6.0.0 Prefatory note

Some of the papers reviewed in the earlier stages of this study (Kissin & Kaley, 1974; Kissin, 1975; Feldman & Boxer, 1979) encouraged the view that cancers of the mouth, larynx and oesophagus might share a common aetiology, in Western countries anyway. If this were true then the three cancers could be mapped together, with the advantage that the larger, aggregate numbers would enhance confidence in mortality ratios and significance test results. Accordingly, the author purchased data on all three cancers from the General Register Office for Scotland. As the literature survey developed, however, it became increasingly obvious that belief in a common aetiology could not be sustained - except at a superficial level - and that it was no longer possible to justify aggregating the data. The alternative, mapping cancers of the mouth and larynx separately, was considered but rejected because of their much smaller numbers. In this way the study came to focus on one cancer only: cancer of the oesophagus. Data on mouth and laryngeal cancers were not entirely discarded, however, as it was thought useful to see if areas which emerged with significantly high mortality from oesophageal cancer also had high rates for other types of cancer. For this reason death rates for cancers of the mouth and larynx, as well as cancer of the oesophagus, were produced (see Table 23): later on, SMRs for mouth and laryngeal cancer are calculated for selected areas (Chapter Seven, section 7).

TABLE 20 & FIGURE 14: SCOTTISH POPULATION BY SEX AND FIVE-YEAR AGE GROUP: 1971



Source: 1971 Census of Scotland

6.1.0 Population structure, Scotland, 1971

The population of Scotland in 1971 was approximately 5.2 million (2.5M males, 2.7M females), heavily weighted in both sexes by the younger age groups. More than half the population in 1971 was below the age of 25: over a third were under 20 years of age (see Table 20 and Figure 14 on facing page).

6.1.1 Overall mortality experience: Scotland compared with England & Wales

With the exception of females in the 10-14 and 20-24 age groups, overall mortality in Scotland is uniformly higher than in England and Wales. In age group 35-39 Scottish men have a 31% higher mortality rate than men in England and Wales. Overall, the mortality of Scottish men is 16% higher, and the women 14% higher, than in England and Wales (Life Tables: Scotland, 1977). Scottish mortality by age and sex, expressed as percentages of the corresponding rates in England and Wales are shown in Table 21 overleaf.

6.2.0 The study population: number of deaths, crude death rates, age-specific death rates, median age at death

The study population consists of all persons dying of oesophageal cancer in Scotland during the years 1970-74.¹ As already explained, limited use is also made of data on deaths from cancers of the mouth and larynx. Table 22 shows the numbers of deaths from each cancer

1. The data were supplied by the General Register Office for Scotland in the form of unpublished computer tabulations giving deaths by sex, age, cause, occupation unit and area code for each of the five years 1970-74.

TABLE 22: NUMBER OF DEATHS BY SEX AND AGE GROUP AND RATES PER ANNUM PER 100 000 POPULATION FOR THREE CANCERS
SCOTLAND 1970-1974

age	ICD 140-149 MOUTH				ICD 150 OESOPHAGUS				ICD 161 LARYNX			
	MALES		FEMALES		MALES		FEMALES		MALES		FEMALES	
	deaths	rates	deaths	rates	deaths	rates	deaths	rates	deaths	rates	deaths	rates
0-4	2	.18	1	.09	-	-	-	-	-	-	-	-
5-9	-	-	-	-	-	-	-	-	1	.09	-	-
10-14	-	-	-	-	-	-	-	-	-	-	-	-
15-19	2	.20	1	.10	-	-	-	-	-	-	-	-
20-24	4	.41	3	.31	1	.10	-	-	-	-	-	-
25-29	-	-	-	-	-	-	-	-	-	-	-	-
30-34	2	.27	-	-	3	.41	-	-	-	-	-	-
35-39	7	.95	1	.13	6	.81	1	.13	-	-	-	-
40-44	5	.66	7	.88	13	1.72	6	.75	5	.66	3	.38
45-49	15	1.91	10	1.21	36	4.59	18	2.17	6	.76	2	.24
50-54	27	3.87	14	1.79	80	11.46	37	4.74	26	3.72	12	1.54
55-59	29	4.05	26	3.19	104	14.53	65	7.97	28	3.91	7	.86
60-64	57	8.52	41	5.15	168	25.12	97	12.18	56	8.37	11	1.38
65-69	79	14.82	55	7.82	198	37.14	143	20.34	65	12.19	14	1.99
70-74	78	22.91	44	7.90	181	53.17	149	26.75	64	18.80	12	2.15
75-79	73	37.10	44	11.60	111	56.42	158	41.66	44	22.36	7	1.85
80-84	57	55.57	47	20.86	81	78.97	137	60.81	19	18.52	10	4.44
85-89	24	58.75	29	29.12	40	97.92	80	80.34	10	24.48	3	3.01
90-94	14	148.15	7	24.50	8	84.66	20	69.99	6	63.49	1	3.50
95+	1	125.00	1	21.51	1	125.00	2	43.01	-	-	-	-
	477	All 3.79	331	All 2.44	1031	All 8.20	913	All 6.73	330	All 2.62	82	All .60

Rates calculated from unpublished mortality data supplied by the General Register Office for Scotland.

by sex and 5-year age group: Figure 15 shows age/incidence curves for the three groups.

TABLE 21: Mortality by age group in Scotland expressed as percentage of rates in England & Wales: 1970-72

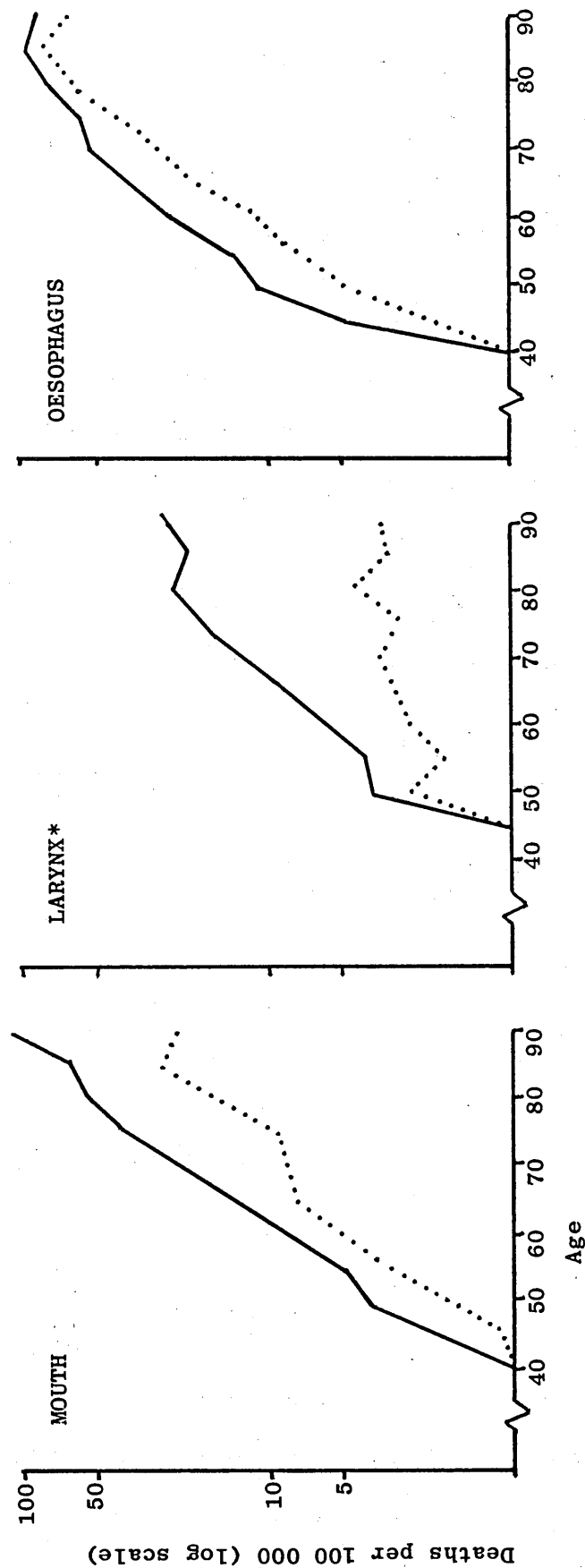
AGE	MALES	FEMALES
0-4	110	111
5-9	115	132
10-14	118	78
15-19	109	107
20-24	110	87
25-29	128	109
30-34	128	123
35-39	131	123
40-44	127	119
45-49	125	125
50-54	124	126
55-59	120	124
60-64	116	123
65-69	114	119
70-74	111	115
75-79	108	113
80-84	104	109
85-89	104	106
90+	105	103

Source: Life Tables 1970-72, HMSO (Edinburgh) 1977.

Over the 5-year period (1970-74) oesophageal cancer deaths in Scotland averaged 206 a year for men and 183 a year for women (rounded figures): crude death rates in the period were 8.21/100,000 per annum for males and 6.73/100,000 per annum for females. Since the 1960s there has been a slow but steady increase and recent data (see Chapter One, section 1.5.4) indicate that oesophageal cancer rates in Scotland now exceed 12/100,000 per annum for males and 9/100,000 per annum for females.

Deaths from cancers of the mouth and larynx were relatively rare: mouth cancer deaths averaged 95 a year (3.79/100,000 per annum) for men and

FIGURE 15: CANCERS OF THE MOUTH, LARYNX AND OESOPHAGUS: SCOTLAND 1970-1974: AGE/INCIDENCE CURVES



Males — Females

* The rates for laryngeal cancer are based on very few deaths (330 male, 81 female): the female rates, in particular, are almost certainly unreliable.

66 a year (2.44/100,000 per annum) for women. Deaths from laryngeal cancer averaged 66 a year (2.63/100,000 per annum) among men and only 16 a year (0.60/100,000 per annum) in women. Rates per 100,000 population by sex and 5-year age group for all three cancers are shown in Table 22.

Although deaths from cancers of the mouth, larynx and oesophagus sometimes occur in early years, all three cancers are typically diseases of late onset.

TABLE 23: Median age at death in three groups of cancer victims: Scotland 1970-74

Cancer Group	Males	Females
mouth	70.44	70.24
larynx	67.12	66.64
oesophagus	67.14	72.50

6.3.0 Oesophageal cancer and occupation in Scotland:
distribution of deaths by occupation order.

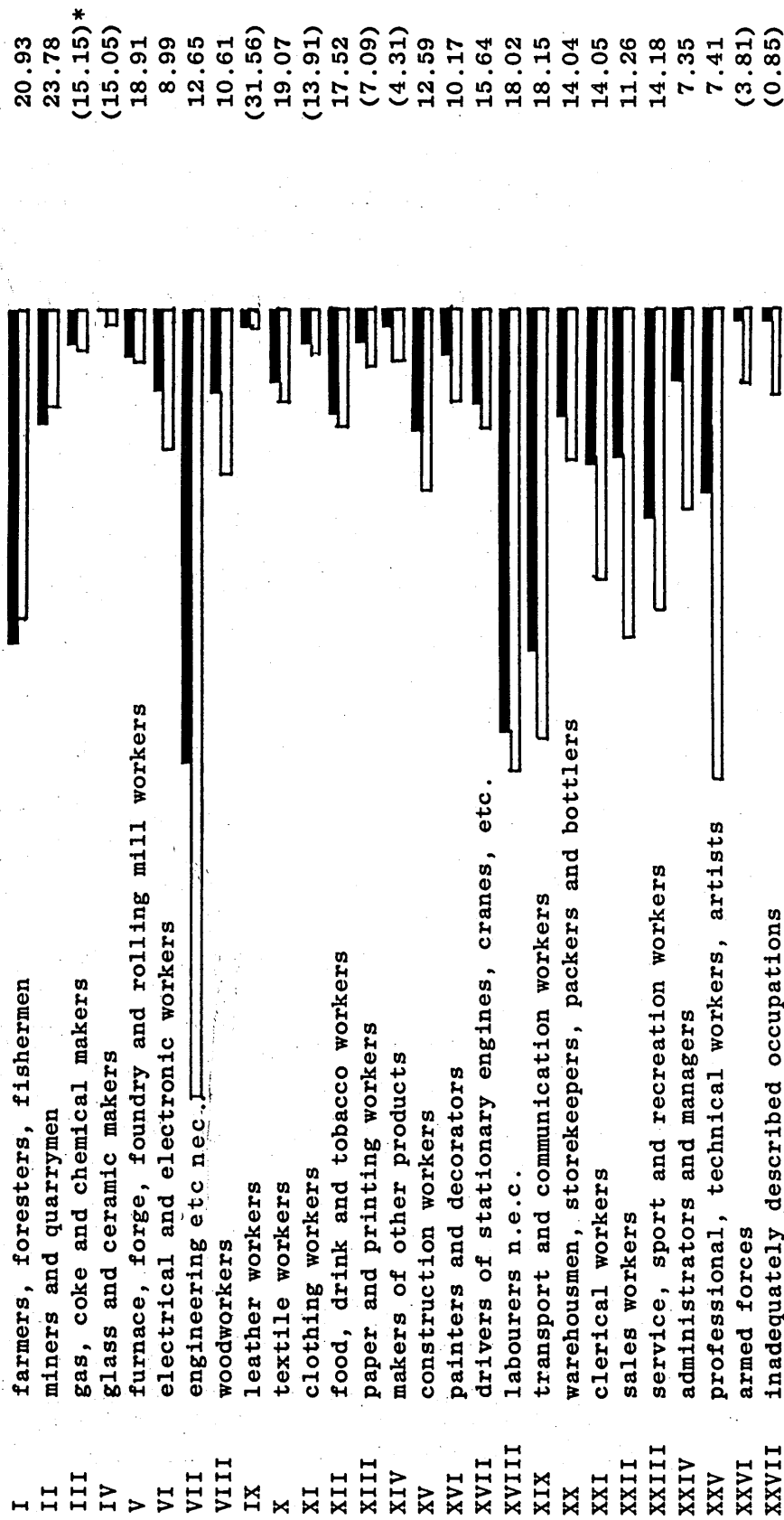
Since 1961 related occupations have been grouped in 27 'occupation orders', these lend the data a quasi-industrial (rather than social or socio-economic) dimension. Examining mortality by occupation order may show whether oesophageal cancer is more prevalent in certain broad categories of work than in others. For reasons given in section 6.3.1, the data below are for male occupation orders only.

As Figure 16 shows, there is a crude correspondence between the number of men and the number of oesophageal cancer deaths in an occupation order. Orders with large populations are, for the most part, associated with numerous deaths, small-population orders with fewer

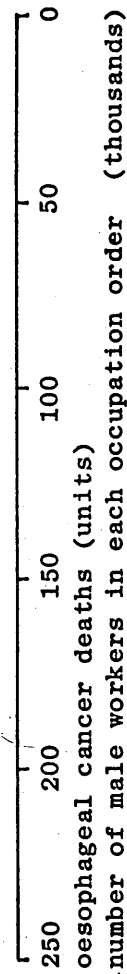
FIGURE 16: MALE OESOPHAGEAL CANCER DEATHS BY OCCUPATION ORDER: SCOTLAND 1970 - 1974

crude annual death rate
per 100 000 population

occupation order



*numbers in brackets are
based on fewer than
ten deaths



deaths. However, within the orders the crude death rates vary considerably: from more than 20/100,000 per annum men in orders I and II (farmers, fishermen, miners, quarrymen), to around 7/100,000 per annum in orders XXIV and XXV (administrative and professional). SMRs for occupation orders were not calculated: to have done so would have required age-specific populations for all 224 occupation units and the purchase of these was ruled out by reason of cost. Instead, SMRs were calculated for selected occupations, as described in the next section.

6.3.1 Oesophageal cancer and occupation in Scotland:
selection of occupation units for analysis:
preliminary remarks and selection criteria

The following analysis is confined almost entirely to the occupations of males. Two serious deficiencies in the data prevent analysis of female occupations in the sample: missing occupation codes and spurious entries. Out of a total of 1,944 entries for oesophageal cancer deaths, 373 (364 female, 8 male), had occupation units entirely missing, while a further 46 units (36 male) were incomplete. Just over 40% of the female sample had occupation units either missing or incomplete, in contrast to the male sample with less than 5% missing or incomplete.

Even if there were no missing entries, however, it would still not be possible to conduct any rational investigation of female occupational mortality. On death certificates, unless a woman is single, widowed or divorced, the occupation recorded will be that of her husband, even

if she had been employed in her own right. This practice - to be deplored both on egalitarian and epidemiological grounds - gives rise to clearly spurious entries. Thus, the female data set used here includes 23 coalminers, 11 carpenters and joiners, 11 railway lengthmen and 6 blacksmiths: unlikely occupations for women in Scotland. There are, of course, specific hazards to the wives and families of men in certain occupations (the bringing home of asbestos or coal dust in clothing, for example) which may have a direct bearing on female mortality. It can also be argued that the pay and status of a man's occupation may affect his wife through such factors as drinking and smoking: the effect of such influences, however, are hard to measure.

Where female occupations are analysed in the following pages, the populations involved comprise - by definition - only single, widowed or divorced women: this introduces a further element of uncertainty. Single status, bereavement and/or separation are known to be risk factors for alcohol abuse in both sexes (Royal College of Psychiatrists, 1979) and perhaps also predispose individuals to the development of cancer. These aspects should be borne in mind when considering the female occupational SMRs presented below.

Because of small numbers population data for some occupations have been amalgamated (by the General Register Office) with those of closely related occupations: disaggregated data for these occupations are not available. This is the reason why the 35 male and 10 female occupations examined in section 6.3.3 below have been condensed into 26 and 4 groups respectively. For the most part the occupations which have been grouped

together are so similar that there can be few objections to looking at their combined mortality experience: in one instance only (the amalgamation of plumbers and heating engineers - units 045-6) might it have been desirable to work with disaggregated data.

Two criteria governed the selection of occupations for analysis:

1. All occupations with 15 or more deaths in 5 years were tested: this admittedly arbitrary figure was chosen to ensure a measure of stability in the rates.
2. Occupations with fewer than 15 deaths in 5 years were considered only if there was a known association with alcohol abuse and/or high cirrhosis mortality, or if occupational exposure to suspected carcinogens (e.g. lead or cadmium) might be involved. (In other words, if there is an a priori assumption that such occupations will show high mortality ratios for oesophageal cancer because they have done so elsewhere.)

6.3.2 Further limitations of the data

1) The 10% Economic Activity Sample

The age-specific populations used here to calculate occupational SMRs are derived from a 10% sample of the 1971 Census. The 10% sample is formed by selecting one household from each run of 10 households, or one person from every 10 persons enumerated in hotels, hospitals and prisons, etc. Although the sample as a whole embraces 10% of the population, for sub-groups within the population the 10% figure is notional. In the case of occupations, the figures reflect the frequency with which a particular occupation has come to light in a 10% sample of the general population:

this may or may not be an accurate reflection of the real numbers. Sampling procedures are designed to eliminate bias but there are a number of areas in which errors can and do occur. The percentage size of sampling and rounding errors varies inversely with the numbers in the sample and this makes analysis of some of the smaller occupation groups somewhat suspect. It is also possible that occupations in which workers tend to cluster in small areas (e.g. fishermen, dockers, railway workers near large termini) may be under-represented in the 10% sample: this matter is referred to again in section 6.3.3 on railway lengthmen.

Ideally, it would be possible to check the accuracy of the 10% sample by comparing corresponding entries in the 100% sample: unfortunately the two are not compatible. The 10% sample covers all age groups over 15 years and thus includes people who have retired from their occupations: the 100% sample lists only the economically active. In each instance the occupational populations in the 100% sample are less than the extrapolated totals in the 10% sample. Sampling and rounding errors are magnified when extrapolating from the 10% sample to give estimates of the 'real' population; such errors may be further magnified in the process of deriving standard populations for the calculations of SMRs. Theoretical limits for sampling and rounding errors in the 10% sample are given in Appendix E of the 1971 Census: Economic Activity Tables: 10% Sample.

2) Occupational descriptions on death certificates

Death certificates not infrequently carry inaccurate occupational descriptions, the origins of which are discussed in section 3.1.1 of Occupational Mortality: The Registrar General's Decennial Supplement for England and Wales, 1970-72 (OPCS/HMSO, 1978) and by Adelstein (1978). Briefly summarised, the causes of inaccuracy are:

- faulty recollection on the part of surviving relations, particularly if these are elderly;
- 'promotion' of the dead person by a surviving spouse or relation (e.g. a hospital orderly described as a 'nurse', or a sales manager as a 'director');
- change of principal occupation for a secondary occupation before retirement (this is a particular problem where an occupation entails early retirement, e.g. the police, armed forces, airline pilots and miners underground).

The later the age at death the less chance of an accurate job description on the death certificate and for this reason occupational SMRs are usually presented for ages 15-64 only (20-64 in some publications).

Late-onset diseases pose problems, however, since the majority of deaths may occur after retirement age. Rather than discard information on deaths among the elderly, some authors use the Proportional Mortality Ratio (PMR). This is derived by direct standardisation in a manner similar to the SMR but, instead of measuring the mortality rate, it compares the proportion of deaths in a group from a particular cause with the distribution of deaths from the same cause in the standard population. However, as remarked in the Decennial Supplement (op cit):

'The proportion for an individual cause may be high because the rate for that cause is high or because the rate for some other major cause is low; the PMR does not allow these causes to be distinguished.' The authors of the Decennial Supplement rate this drawback as limited in importance and use the PMR alongside the SMR throughout.

The present author has preferred to calculate two SMRs for each cause, one for age 15 and over, the other for ages 20-64. This approach was used in Occupational Mortality 1968-73 (HMSO Edinburgh, 1981) and - since the present study is concerned with cancer mortality in Scotland - consistency with the Scottish publication was thought useful and desirable. With a late-onset disease there is a risk that the researcher will end up with two sets of SMRs, neither of which is reliable and between which there is wide disagreement. In the event there proved to be a remarkably good agreement ($r = 0.96$) between the two sets of SMRs produced here (see Table 24). Although there were a few large discrepancies (e.g. the SMRs differ by 91% in the case of metal platers (unit 035)), these mostly occur among the small occupational units and are probably just chance effects: there appears to be no overall relationship between the size of an occupational unit and the percentage disagreement between the two SMRs for that unit ($r = 0.06$).

TABLE 24: OESOPHAGEAL CANCER MORTALITY BY SELECTED OCCUPATIONS: SCOTLAND 1970-1974

Occupation	Code	Population in 10% Sample	SMRs (ages 15 and over)			SMRs (ages 20-64)		
			Obs.	Exp.	Signif.	Obs.	Exp.	Signif.
MALES								
railway lengthmen	106	359	21	4.04	<.001	9	1.29	698 <.001
stevedores	133	464	11	4.25	<.005	5	1.56	320 <.05
textile workers	072-3	464	6	2.64	-	3	1.13	265 -
fishermen	001	1 018	16	7.56	<.005	3	1.96	153 -
deck & engine room ratings	116	502	8	3.90	<.05	3	1.15	261 -
other metal making (nec)	054	1 890	16	8.95	<.005	8	4.90	163 -
bakers and pastrycooks	178	985	13	6.88	<.05	6	2.97	202 -
plumbers etc	045-6	2 186	11	7.07	-	7	3.61	194 -
brewers etc	080	357	3	1.94	-	2	0.85	235 -
goods vehicle drivers	122	6 102	33	24.46	-	20	13.54	148 -
machine tool operators	031-2, 039	3 147	17	12.12	-	8	5.90	136 -
painters and decorators	100	2 406	13	10.42	-	10	5.50	182 -
maintenance engineers	042-3	7 459	34	27.80	-	14	8.27	169 -
shop salesmen	144	1 686	10	8.42	-	4	3.08	130 -
gardeners	005	1 508	17	16.23	-	4	5.08	79 -

(continued below...)

(males, continued...)

agricultural workers	003	3 440	28	27.26	103	-	13	8.18	159	-
clerks and cashiers	138-141	8 373	51	52.80	97	-	27	20.68	131	-
carpenters	055	4 090	16	18.82	95	-	4	7.53	53	-
warehousemen	136	4 375	28	29.51	95	-	12	13.21	91	-
engineers	109	2 910	18	20.79	87	-	6	8.77	68	-
farmers	002	3 567	32	37.46	85	-	9	9.99	90	-
proprietors and managers	143	4 362	28	33.56	83	-	8	13.70	58	-
coalminers underground	007	3 143	26	31.36	83	-	9	9.64	93	-
building workers	113	2 910	12	19.43	62	-	6	10.30	58	-
metal platers	035	1 374	6	9.89	61	-	1	3.11	32	-
teachers	193-4	4 919	6	14.66	41	<.05	3	7.09	42	-

FEMALES

domestic housekeepers	156-8	933	23	7.44	308	<.001				
maids	164	1 266	11	6.71	164	-				
proprietors	143	3 895	21	15.38	137	-				Female numbers in
teachers	103-4	7 048	16	15.19	105	-				20-64 age group too
clerks and cashiers	139-141	15 572	36	34.22	105	-				few for analysis.

Sources: Population data from Occupational Mortality 1969-1973 (Registrar General for Scotland, 1981)

Mortality data: Registrar General for Scotland, unpublished computer tabulations,

6.3.3 Analysis of oesophageal cancer mortality in selected Scottish occupation units: occupations with high SMRs

NB: In the following pages all references to Scottish occupational SMRs, other than those for cancers of the mouth, larynx and oesophagus, are taken from Occupational Mortality: 1968-73 (HMSO Edinburgh, 1981). SMRs for occupations in England and Wales are from Logan (1982),² unless otherwise stated. SMRs will usually be quoted in pairs: first the SMR for ages 15 and over, then (in brackets) the SMR for ages 20-64. Significance values relate to the SMRs for ages 15 and over, unless otherwise stated.

Unit 106: Railway lengthmen: SMR 520 (698), $p < .001$

There is nothing obvious which might account for the extraordinarily high SMRs for railway lengthmen in Scotland. It is just possible that the 10% sample failed to 'net' anything approaching 10% of lengthmen and that, in reality, their numbers are far larger than the sample suggests. Unfortunately, it is not possible to check the numbers against the 100% economic activity totals, partly because different age ranges are involved but mainly because, in the 100% sample, occupation unit 106 is aggregated with five other units. Even increasing the nominal size of the lengthmen sample by twice the standard error³ only results in the SMR (ages 15+) falling to around 470: still very high.

-
2. Logan's time series extends almost to the beginning of the present century and permits a wider range of historical comparisons than the 1970-72 Decennial Supplement.
 3. Appendix 'E' of the 1971 10% Sample gives the standard errors for a range of sample sizes. Extrapolating from the figures given, the standard error for a sample of 359 (the number of lengthmen in the 10% Sample) would be about 19.

The proportion of pre-retirement deaths among lengthmen (43%) differs only slightly from that in the sample as a whole (40%): nevertheless, there are some unusual aspects to the age structure of the group. In the total data set there were only three deaths in men aged 30-34, yet two of them were railway lengthmen. As a group the lengthmen died appreciably earlier than the average: the median age at death in the group was 60.73 years, compared with 67.14 years for all males in the sample.

Nor are the lengthmen unique among railway workers for their high mortality indices. North and south of the border railwaymen have high SMRs for cancers, though none so high as the Scottish lengthmen. Scottish railway drivers and motormen (unit 118) have an overall (i.e. 'all causes') SMR of 144 (123): for all malignant neoplasms their SMR is 139 (132) and for cancer of the trachea, bronchus and lung their SMR is 158 (138). Historical data for England and Wales (see note at beginning of section) show that railway porters have had consistently high indices for all cancers and particularly for cancer of the oesophagus: in 1911 their SMR (ages 20-64) for this cancer was 156, in 1971 it was 183.

Units 133, 001 and 116: Stevedores, fishermen, deck and engine room ratings

Oesophageal cancer SMRs for all sea-related occupations in Scotland are high: for stevedores and fishermen the ratios also have a high level of statistical significance (which, however, may be slightly spurious,

for reasons given below).

TABLE 25: Oesophageal cancer SMRs in three sea-related occupations: Scotland 1970-74

Unit	Occupation	SMR	Significance
133	Stevedores	258 (320)	$p < .005$
001	Fishermen	212 (153)	$p < .005$
116	Deck & Engine room Ratings	205 (261)	$p < .05$

(Full details in Table 24)

The raised oesophageal cancer mortality observed among seamen and shore workers was not unexpected in view of the alcohol/cancer association and the known propensity of these groups to indulge in alcohol abuse (referred to in Chapter Three, section 3.5.7). However, as well as the several and genuine reasons for high mortality among seafarers, their SMRs for whatever cause are likely to be raised because of under-representation in the Census (a problem noted and discussed as early as the 1931 Decennial Supplement on Mortality). The reverse problem - that of over-representation - affects the Scottish Sea Fisheries Statistical Tables (SSFST): these record the numbers of fishermen in every port and creek along the Scottish coast. However, the boats surveyed may have hired and brought in crews from other ports, or even other countries, and this is known to inflate the figures (Rix et al, 1982). The SSFS Tables consistently record numbers of fishermen between 10 and 15 per cent higher than those recorded by the Census. Between the under-recording of the Census and the over-estimates of the SSFS Tables there are no accepted estimates of the numbers of fishermen and so, for want

of better, the Census figures are used here. The age-specific data used here to derive SMRs for the fishing industry are therefore based upon an acknowledged - but unquantified - under-estimate of the fishing population. The same problem affects estimates of the numbers of deck and engine room ratings - along with fishermen they are under-recorded at Census time because many are at sea.⁴

Although under-recording may result in slightly inflated SMRs (because the true number of deaths is being related to an under-size population), this is unlikely to be the only, or even the most important, factor in the high SMRs observed for these three occupations (i.e. units 133, 001 and 116). SMRs for fishermen are uniformly high: for all causes their SMR is 122 (147) and for stomach cancer it is 159 (146). For deck and engine room ratings the SMRs are: all causes 173 (237), stomach cancer 234 (198) and respiratory-system cancers 196 (243). SMRs for stevedores (who are not under-recorded at Census) are also very high: all causes 177 (168), stomach cancer 134 (162), cancers of the respiratory system 215 (191). Compare these high SMRs with those of men in occupation unit 115 (deck and engineering officers, ships' pilots): here the mortality indices are only just above average, and in some cases below average (all causes SMR 106 (112), stomach cancer 100 (71), cancers of the respiratory system 91 (115). The recording of numbers of men in unit 115 will be similarly affected by absences at Census time, yet their SMRs are by no means high. There appears to be a class factor involved,

4. The fact of under-reporting at Census also raised the possibility of under-reporting of deaths at sea; this led the author to make enquiries about the reliability of the notification process. The General Register Office, however, could find no instance of a subsequently reported failure to notify the relevant authority of a death at sea. (D.Salmond, Vital Events Statistician, General Register Office for Scotland. Personal communication, 1985).

with men in the higher socio-economic class having a better mortality experience than those in the occupations associated with lower socio-economic groupings. The class effect in these results probably points to the influence of excessive alcohol and tobacco consumption in the more seriously affected groups. Lifetime differences in diet may also be involved.

The effects of oesophageal cancer among fishermen upon oesophageal cancer mortality in Scottish coastal towns is considered from a geographical viewpoint in the next chapter.

Units 172-3: Textile workers: SMR 227 (265)

There were a number of reasons for believing that oesophageal cancer mortality among textile workers might be above average. In England and Wales male textile workers have a high mortality from liver cirrhosis (SMR 300 (Donnan & Haskey, 1977)), indicating a heavier than normal use of alcohol in this group. There were also grounds for suspecting that fibres or chemicals used in bleaching might be involved in oesophageal carcinogenesis (Hunter, 1978). As it happens, oesophageal cancer mortality among male textile workers in Scotland is indeed high, but the small number of deaths produce a statistically non-significant result.

Unit 054: Other metal making nec:⁵ SMR 201 (163)

Overall mortality for this unit in Scotland is raised, but not unduly so (all causes, SMR 124 (102)). Cancer mortality, however, is high: all cancers, SMR 139 (117), stomach cancer 136 (134), respiratory cancers 162 (127). The oesophageal cancer SMR of 201 is statistically significant at the $p < .005$ level, but ratios for cancers of the mouth and larynx accord with expectation. Unit 054 embraces a miscellany of occupations, described as 'other metal making and working, jewellery, electrical process and production workers'. The variety of jobs makes it difficult to pinpoint any particular high-risk groups, or to focus on possible causal agents.

Unit 078: Bakers and pastrycooks

The overall mortality experience of bakers and pastrycooks is poor (SMR - all causes - 149) and SMRs for most cancers are rather high: however, there seems nothing specific to the job itself which might account for the high oesophageal cancer ratio (SMR 189, $p < .05$). Cancer mortality among kitchen workers generally is rather high: cooks in Scotland had a male stomach cancer SMR of 176 in 1971; for cancers of the respiratory system (ICD 160-3) the SMR was 204. Cooking is a high-stress, low-pay occupation and alcohol problems appear endemic to kitchen workers (Plant, 1974). In England and Wales cooks have provided some of the highest mortality ratios for liver cirrhosis (1961 SMR 460 (Donnan & Haskey, 1977), 1971 SMR 354 (OPCS, 1978)). The prevalence of lung cancer and the very high indices for cirrhosis point to tobacco

5. Not elsewhere classified.

and alcohol as the most obvious causal agents for oesophageal cancer among cooks.

Units 045-6: Plumbers, lead burners, pipe fitters and heating engineers

The SMR for the two units combined was high (156 (235)) but not statistically significant. However, all the deaths occurred in one unit (045 - plumbers) and had it been possible to calculate the SMR of this unit alone the result would certainly have been higher and would probably have had statistical significance. The reasons why it was not possible to calculate the SMR of plumbers only were described in Chapter Five (section 5.1.4). A significantly high SMR for plumbers in Scotland would contrast with the situation in England and Wales, where SMRs for this occupation have fallen over the years, from 171 in 1911 to 92 in 1971.

Unit 080: Brewers and wine makers, etc.

Alcohol production in Scotland is discussed at greater length in the next chapter: here it is sufficient to say that the number of workers and the number of oesophageal cancer deaths in this occupation are very small and the SMR is devoid of statistical significance.

Units 156-8 and 164: Housekeepers, domestics and maids

Between them, these four occupation units embrace proprietors and managers of boarding houses and hostels, housekeepers, stewards, matrons and housemothers, domestic housekeepers, maids, valets and related

service workers. Whether married or single the women in these groups have a very poor mortality experience. Unit 158 (domestic housekeepers, etc) in particular suffers high mortality from all causes so that neither the SMR for oesophageal cancer nor its high level of statistical significance are surprising, both are consistent with the overall picture shown below:

TABLE 26: Mortality among domestic housekeepers in Scotland (unit 158 - female). SMRs are for ages 15 and over (those in brackets for ages 20-64).

	Married	Single
All causes	165 (301)	239 (162)
All cancers (ICD 140-209)	257 (383)	230 (162)
Cancer of the trachea, bronchus and lung	201 (174)	229 (155)
Cancer of the oesophagus	308	

Cooks, housekeepers and other domestics have high rates for alcoholism and liver cirrhosis (Plant, 1979). Occupations which appear to foster excessive drinking may have certain features in common, among which are access to alcohol, low status, poor job satisfaction, absent or inadequate supervision and solitary working conditions for much of the time (Plant, op.cit.): many of these criteria would seem to be met in the case of cooks and domestics. Evidence of heavy drinking and the high SMRs for respiratory cancers point to tobacco and alcohol as the likeliest causal agents for oesophageal cancer among females in these groups. However, as will already be apparent, Scottish mortality statistics are nothing if not inconsistent! Despite the high rates for cancers in general and for cancer of the oesophagus in particular, there was not one death from laryngeal cancer among these groups in 1970-74, and the ratio for mouth cancer is very near expectation.

6.3.4 Occupations with low SMRs

Units 002-3 and 007: Farmers, agricultural workers and coal miners underground

Farmers and coal miners provide exceptions to the usual pattern of high oesophageal cancer ratios among manual workers: moreover, there is some consistency between the picture in Scotland and that in England and Wales.

TABLE 27: Oesophageal cancer SMRs for farmers and coal miners

	Scotland 1970-74	England & Wales 1971
Farmers	85	93
Coal face workers	83	77

Unit 002 includes farm owners and farm managers, both allocated to social class II. However, a large proportion of farmers in England and Wales, and the majority of farmers in Scotland, operate family farms for which they themselves provide the main labour force. Although incomes may differ, the occupation of a small farmer is not significantly different from that of an agricultural worker (predominantly social classes IIIM and IV) in a larger enterprise.

Oesophageal cancer mortality among Scottish agricultural workers is slightly higher than that for farmers, but still scarcely higher than the average for the whole population (SMR 103). The situation in England and Wales is different: there, agricultural workers have a mortality ratio similar to that of manual workers in general (SMR (E+W) 152). There is no ready explanation for the low oesophageal cancer mortality

among farmers, nor for the large difference in ratios between farm labourers north and south of the border. With an occupational population of more than 34,000 in Scotland, and nearly 30 deaths in 5 years, the difference is unlikely to be due to mere chance.

Coal miners present even more of a puzzle. Oesophageal cancer rates for coal face workers have been subject to extreme fluctuations in England and Wales for much of this century: the SMR for this group was as low as 37 in 1911, rising to 115 in 1951, before falling to 77 in 1971. The low oesophageal cancer ratios for miners contrast with the high ratio for all causes (SMR (Scotland) 148) and the very high ratio for stomach cancer (SMR 171 in England, Wales and Scotland).

It may be possible to shed indirect light on the low oesophageal cancer rates among miners by examining respiratory cancer mortality among different groups in the industry. The groups chosen are: face workers (unit 007), workers below ground nec (unit 009 - this unit includes pit safety workers and persons responsible for lifts, transport and ventilation), and surface workers nec (unit 010 - this unit also includes people working in quarries as well as mines). All mineworkers are forbidden to smoke underground and are, therefore, non-smokers at least for the working day. Face workers are, however, exposed to coal dust to a greater extent than underground safety and maintenance engineers and this is reflected in their higher mortality from respiratory diseases, including cancer. Face workers have a respiratory cancer SMR of 124, but that of workers in unit 009 is only 72. On the other hand, surface

workers in mines and quarries (unit 010), for whom the non-smoking regulations may not be so stringent, have a far higher mortality from respiratory cancers than either of the underground groups (SMR 158 (182 for ages 20-64)).

It is also quite likely that miners do not abuse alcohol to the same extent as some other groups of manual workers. There is a body of evidence to show that occupations with high peer-group status and good wages are not as affected by alcohol abuse as jobs without these attributes (Plant, 1979). Face workers enjoy prestige⁶ and comparatively high wages, added to which they feel a strong sense of corporate or community identity and a need for each to be 'his brother's keeper' below ground. Such factors discourage alcohol abuse and this may account for the fact that miners do not appear in either the 1961 or 1971 lists of occupations with high cirrhosis mortality (Donnan & Haskey, 1977: OPCS, 1978).

If tobacco and alcohol are, as many believe, the principal determinants of oesophageal cancer in the West, then the evidence offered above, although circumstantial, is consistent with the finding of a low mortality from the disease among miners.

6. The prestige enjoyed by miners is reflected in their slight over-representation at Census or on death certificates. Wives in particular are likely to record that their husbands are or were miners even if the husband had changed his job before retirement or death (Decennial Supplement, OPCS 1982): this over-representation favours a slight under-estimate of mortality.

Unit 035: Metal platers

Oesophageal cancer mortality among metal platers was examined because of the possibility that exposure to toxic metals might have produced high rates. In the event, however, the metal/cancer hypothesis received no support from this particular result: not only was the SMR not high, it was actually very low (though small numbers deprived the result of statistical significance). The probability that this result is due to chance is enhanced by the fact of an overall high mortality for metal platers and their very high indices for other cancers. SMRs for metal platers in Scotland in 1971 were: all causes 144, all malignant neoplasms 162 and respiratory-system cancers (ICD 160-3) 202. SMRs for cancers of the mouth and larynx were also high, though at a low level of statistical significance:

TABLE 28: Mortality among metal platers: three cancers

Cancer	Observed Deaths	Expected Deaths	Male SMR (Ages 15+)	Significance
Mouth	9	4.70	191	p < .05
Larynx	7	3.16	222	p < .05
Oesophagus	6	9.89	61	-

Units 221-2: Armed forces: four male deaths, SMR not calculated

The small number of oesophageal cancer deaths among servicemen in Scotland is very unexpected. The service population is large (nearly 23,000 in 1971) and indices of mortality are generally high (male SMR - all causes - 141, all malignant neoplasms 149, and cancer of the trachea, bronchus and lung, 159). Mortality from other upper-alimentary

tract cancers among Scottish servicemen is also low: there were only two deaths from cancer of the mouth in 1970-74 and none from laryngeal cancer. In contrast, oesophageal cancer SMRs for servicemen in England and Wales have for some years been exceedingly high: 338 in 1961, 289 in 1971 (Logan, 1982).

6.3.5 Oesophageal cancer and social class in Scotland

In section 6.3.3 it was pointed out that fishermen, stevedores and engine room ratings have a worse mortality profile than sea-going officers and pilots, and it was suggested that some class-influenced aspect of lifestyle might be involved. To see if there were indeed differences in oesophageal cancer mortality between the classes, the author assigned all males in the sample to a social class on the basis of their occupations and calculated SMRs for each class.⁷ It should be said at once that this approach is intrinsically flawed and that the figures derived are only approximations: nevertheless, the results are not so imprecise as to invalidate the exercise.

Henry (1981) writes: 'Though some reservations have been expressed about the use of a single variable (occupation), it is almost the sole criterion of social class used in British empirical research. This is because no better method has been found...' The chief problem in assigning people to a social class on the basis of their occupation alone is that their status within that occupation does not show in the statistics. For example, a self-employed forester is assigned to

7. Tables of SMRs by social class in Scotland are available for the major causes of death: oesophageal cancer, however, is not included.

TABLE 29: MALE OESOPHAGEAL CANCER DEATHS BY SOCIAL CLASS: SCOTLAND 1970-74

Social class	1971 population of economically active and retired males (10% sample)	Observed deaths	Expected deaths	SMR	Significance
I	7 246	29	34	85	-
II	25 245	129	178	72	p<0.005
III(N)	15 945	80	95	84	-
III(M)	63 638	363	327	111	p<0.05
IV	31 208	256	208	124	p<0.001
V	17 275	121	119	102	-
Not classified*	6 846	53	71	75	p<0.05
Total	168 885	1 031	1 032**		

* See text.

** Actual number 1 031: discrepancy probably due to rounding procedure.

Source: Population data are from Table 29, 1971 Census of Great Britain, Economic Activity Part IV: 10% Sample.

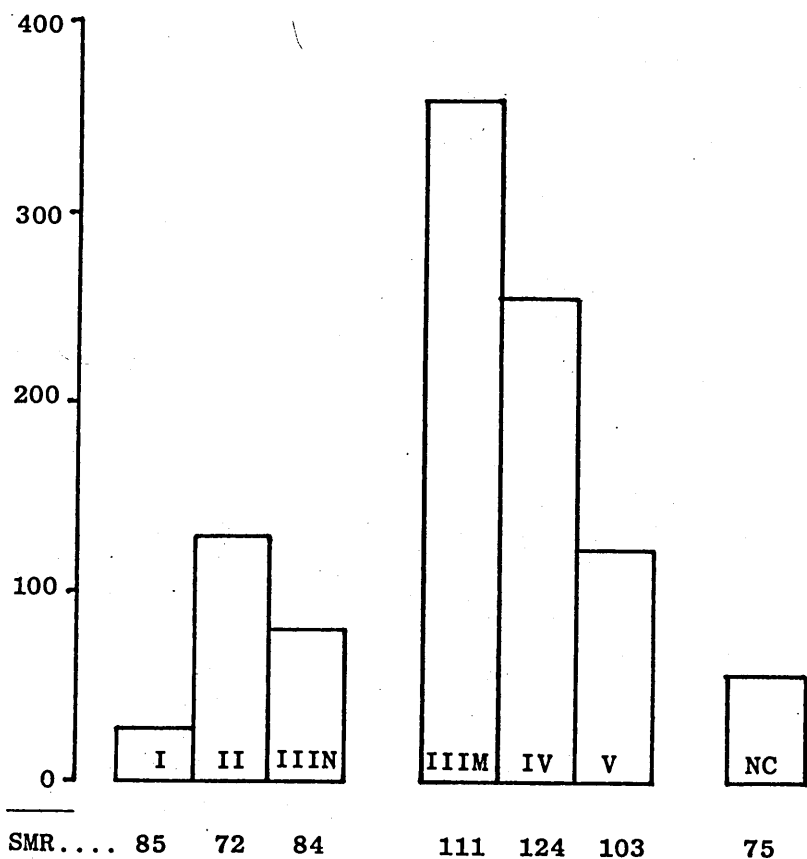
social class II, but a foreman forester occupies class IIIM and an apprentice or family employee in forestry is placed in class IV. In the following exercise it has been assumed that the majority of people in work are employees, rather than self-employed or employers. The social class appropriate to employee status is therefore used in all but those occupations in orders XXIV (administrators and managers) and XXV (professional, technical workers and artists). Occupations have been placed in social classes in accordance with the system devised by National Opinion Polls (1972). Among others, persons with inadequately described occupations (unit 223), entries with missing or incomplete occupation codes and members of the armed forces are not assigned a social class⁸ and are included in the 'not classified' category. The SMR for males in this group is rather low (SMR 75, $p < 0.05$), perhaps because of the unexpectedly small number of oesophageal cancer deaths in the armed forces (mentioned above).

To a large extent the distribution of deaths reflects the 3.3:1 preponderance of manual over non-manual workers in the Scottish working population: however, the SMRs show that there are in fact significant differences in oesophageal cancer mortality between the social classes. The three non-manual classes all had SMRs below 100: class II was significantly low. Two of the three manual classes had significantly high SMRs. In line with expectation - and in the light of the class-influenced drinking and smoking habits discussed in Chapters Three and Four - social classes III(M) and IV (skilled and partly-skilled

8. M. Hay, General Register Office, personal communication, 1986.

occupations) emerged with the highest SMRs. Social class V (unskilled occupations) might have been expected to show a similarly high mortality but the SMR for this class was very near expectation. There is no firm evidence to suggest why this should be so: the hypothesis that low incomes act as a curb on alcohol consumption does not appear to stand up to investigation.

Figure 17: Distribution of male oesophageal cancer deaths among social classes in Scotland, 1970-1974.



6.4.0 Brief summary

No specific occupational hazards (e.g. fibres, dusts or toxic hazards) emerge from the analysis of occupational mortality. The only consistently observed relationship in this chapter is between the disease and social class, with the highest mortality occurring among manual workers. In the absence of any clear pointers to the contrary, excess drinking and smoking, probably in conjunction with dietary inadequacies, continue to be the likeliest causal factors.

CHAPTER SEVEN: THE GEOGRAPHICAL DISTRIBUTION OF OESOPHAGEAL CANCER
IN SCOTLAND: 1970-74

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CHAPTER SEVEN: THE GEOGRAPHICAL DISTRIBUTION OF OESOPHAGEAL CANCER
IN SCOTLAND: 1970-74

7.0.0 Introduction

In the previous chapter the distribution of oesophageal cancer was discussed in relation to the age, occupation and social class structure of the Scottish population: this chapter examines the spatial distribution of the disease. The areal units used for the spatial analysis are those which were supplied with the mortality data, namely the pre-1975 local government areas. Standardised mortality ratios (SMRs) are calculated for each urban area and for groups of rural areas (see definitions below): results are mapped for each sex separately. SMRs are also calculated for each type of local government area (i.e. city, large burgh, new town, etc) to produce an urban/rural mortality gradient. Areas with significantly high SMRs in either sex were investigated further to see if the raised mortality was distributed generally or present in high-mortality foci.

In the previous chapter sea fishing and dock work were identified as high-risk occupations for oesophageal cancer. In section 7.7.1 data from the coastal small burghs are examined to see if the presence or absence of the fishing industry is reflected in the mortality indices. Alcohol-producing areas come under scrutiny in section 7.7.4 and there is a brief reference to the jute industry in section 7.7.5.

Finally, in section 7.8.0, areas with significantly high mortality from oesophageal cancer are investigated for high levels of other cancers. Five areas emerged with significantly high SMRs for three or more cancers: these are identified and discussed.

7.1.0 Pre-1975 local government areas in Scotland

Prior to the 1975¹ reorganisation of Scottish local authorities there were 399 local government areas distributed among 33 counties. The local government areas consisted of four cities (referred to as 'Cities of Counties', abbreviated to 'CC'), 21 large burghs (LBs), 176 small burghs (SBs) and 196 rural areas (described as 'Districts of Counties', or 'DCs'). As well as the original 399 local government areas, five new towns (NTs) were created by administrative amalgamation of small burghs and their adjacent rural districts. The 1971 Census published data for the NTs as a whole and also included data on the SBs and DCs from which the new towns were created.

Officially, the pre-1975 local government areas were defined according to population size, as follows:

Cities	100,000 population and over
Large burghs	20,000-99,999
Small burghs	1,000-19,999
New Towns	No specified limit
Districts of County	No specified limit

In practice, the populations of the old administrative areas seldom conformed to the official system. Some local authorities failed to keep

* 1974 in England and Wales

pace with population change and did not apply for the status appropriate to their new size (Bartholomew, 1970). A few areas - designated as small burghs - do not come near the minimum size laid down and are in fact little more than villages. Apart from the cities, which are in a class of their own for size, there is a confusing amount of overlap between the other three urban categories and the labels LB, SB and NT cannot automatically be taken as indicators of population size. As an example: Bearsden (the largest small burgh) had a population 75 times that of the smallest small burgh and was also bigger than some of the large burghs and new towns.

7.2.0 General comments on the methods used in the spatial analysis

In the following analysis male and female oesophageal cancer SMRs are calculated for each of the cities, large burghs and new towns, and for groups of rural areas. The rural areas consist of small burghs and districts of county grouped according to the criteria set out in Appendix 1 at the end of this work. For the present, it should be said that the rural areas were grouped, where possible, in such a way as to provide populations of around 50,000 in either sex: this was done to reduce the effects of chance variations on the death rates. Wherever possible rural areas with similar characteristics were also grouped together. Thus, predominantly lowland areas were combined for analysis and not mixed with upland areas: coastal areas were treated separately from areas inland.

A decision was made not to use the standard regions for investigating mortality patterns, although the General Register Office could have supplied the data by standard region on request. Some of the standard regions in Scotland have such large populations and contain such dissimilar geographical features that there was a strong possibility that significant local variations in mortality could get smoothed out, or their association with a particular feature might escape notice.

Gardner et al (1983) also rejected the standard regions and chose local government areas for their Atlas of Cancer Mortality in England and Wales, 1968-1979.

A propos the tabulated results of the analysis:

1. In all of the tables chi-squared statistics lower than the critical value of 3.84 ($p < 0.05$ with one degree of freedom) are omitted.
2. Where expected values are less than five the chi-squared test is not used: instead, significance levels are calculated using the Poisson distribution (see Appendix 1 for a discussion of the rationale behind the choice of significance test).
3. In a very few instances published totals in the Census do not agree with the totals derived from summing the populations of each age group: this is because of rounding. In the present work all area totals agree with the totals arrived at by summing their age groups and for this reason the reader may notice some slight differences between the author's totals and those in the 1971 Census. Agreement between age-group totals and final totals was necessary to the functioning of the computer program which produced the SMRs.

7.3.0 Distribution of oesophageal cancer by local government area

Part 1: Tables

Table 29: Distribution of oesophageal cancer deaths in Scotland by local government area. The four cities.

City	Sex	Population 1971	Observed deaths (-- 1970-1974 --)	Expected deaths	SMR	Chi ²	Significance level
Aberdeen	M	84 680	36	37.35	96	-	-
	F	97 390	43	36.58	118	-	-
Dundee	M	86 170	53	34.09	155	10.49	<0.01 (+)
	F	96 040	48	34.00	141	5.77	<0.05 (+)
Edinburgh	M	211 400	108	94.55	114	-	-
	F	242 180	96	97.03	99	-	-
Glasgow	M	429 100	182	170.58	107	-	-
	F	468 385	161	156.89	103	-	-

In this and the following tables (+) indicates a significantly high result and (-) a significantly low result.

Table 30: Distribution of oesophageal cancer deaths in Scotland by local government area.

The 21 Large Burghs.

Burgh	Sex	Population 1971	Observed deaths (1970-1974)	Expected deaths	SMR	Chi ²	Significance level
Airdrie	M	18 290	5	5.83	86	-	-
	F	19 435	9	4.64	194	-	p<0.05 (+)
Arbroath	M	10 715	3	4.43	68	-	-
	F	11 860	7	4.54	154	-	-
Ayr	M	22 190	15	10.32	149	-	-
	F	25 710	14	9.74	144	-	-
Coatbridge	M	25 330	7	8.27	85	-	-
	F	26 810	6	6.52	92	-	-
Clydebank	M	23 395	7	8.42	83	-	-
	F	24 885	7	6.65	105	-	-
Dumbarton	M	12 495	3	4.54	66	-	-
	F	13 150	8	3.81	210	-	p<0.05 (+)
Dunfermline	M	24 615	7	9.43	74	-	-
	F	25 290	14	7.93	177	4.65	p<0.05 (+)
Dumfries	M	13 990	6	5.36	112	-	-
	F	15 385	4	5.39	74	-	-
E.Kilbride	M	31 260	15	6.98	215	9.23	p<0.01 (+)
	F	32 240	7	5.47	125	-	-

Table 30 continued...

Falkirk	M	18 130	11	8.24	134	-	-
	F	19 445	3	6.60	45	-	p<0.05 (-)
Greenock	M	33 750	18	13.05	138	-	-
	F	35 745	16	11.23	143	-	-
Hamilton	M	22 320	4	7.71	52	-	p<0.05 (-)
	F	24 015	9	6.14	147	-	-
Inverness	M	16 420	9	6.97	129	-	-
	F	18 415	7	6.65	107	-	-
Kilmarnock	M	23 275	7	8.77	80	-	-
	F	25 520	10	7.36	131	-	-
Kirkcaldy	M	23 845	8	10.78	74	-	-
	F	26 515	12	9.31	129	-	-
Motherwell & Wishaw	M	35 595	12	13.77	87	-	-
	F	38 065	7	11.15	63	-	-
Paisley	M	45 285	15	17.01	88	-	-
	F	50 075	15	16.50	91	-	-
Perth	M	20 415	13	9.22	141	-	-
	F	22 615	6	8.33	68	-	-
Port Glasgow	M	10 825	4	3.33	120	-	-
	F	11 575	2	2.60	77	-	-
Rutherglen	M	11 645	5	4.48	112	-	-
	F	13 080	7	4.34	161	-	-
Stirling	M	14 705	6	5.63	107	-	-
	F	15 705	4	5.17	77	-	-

Table 31: Distribution of oesophageal cancer deaths in Scotland by local government area.

Rural areas.

	County or county group	Sex	Population 1971	Observed deaths (1970-1974)	Expected deaths	SMR	Chi ²	Significance level
(1)*	Orkney & Zetland	M F	16 475 17 335	10 3	8.89 7.52	113 40	- -	- p<0.05 (-)
(2)	Caithness Ross & Cromarty Sutherland	M F	48 995 50 750	15 12	25.09 19.82	60 61	4.06 -	p<0.05 (-) -
(3)	Banff Moray Nairn	M F	52 905 53 120	35 20	22.68 19.72	154 101	6.69 -	p<0.01 (+) -
(4)	Aberdeen	M F	67 465 70 430	37 21	31.89 25.24	116 83	- -	- -
(5)	Argyll Bute Inverness	M F	61 915 69 990	27 25	33.52 29.68	81 84	- -	- -
(6)	Angus Kincardine	M F	48 470 52 265	26 20	24.61 21.99	106 91	- -	- -
(7)	Perth	M F	40 900 43 175	21 23	21.68 18.55	97 124	- -	- -
(8)	Dunbarton	M F	87 715 100 640	28 22	27.62 24.45	101 89	- -	- -
(9)	Fife	M F	80 420 86 640	34 33	37.25 31.70	91 104	- -	- -

Table 31 continued...

(10)	Clackmannan Kinross Stirling	M	95 230	35	35.86	98	-	-
		F	98 365	23	28.28	81	-	-
(11)	Renfrew	M	84 375	22	31.18	71	-	-
		F	90 655	28	27.17	103	-	-
(12)	Lanark	M	160 185	41	57.69	71	4.84	p<0.05 (-)
		F	168 455	46	46.35	99	-	-
(13)	East- Mid- West Lothian	M	157 415	52	55.79	93	-	-
		F	162 870	28	43.55	64	5.55	p<0.05 (-)
(14)	Ayr	M	130 865	40	53.96	74	-	-
		F	142 850	37	46.13	80	-	-
(15)	Berwick Peebles Roxburgh Selkirk	M	46 050	21	24.56	84	-	-
		F	51 505	17	22.81	75	-	-
(16)	Dumfries Kirkcudbright Wigtown	M	55 525	14	26.30	53	5.75	p<0.05 (-)
		F	58 925	29	21.81	133	-	-

* The numbers in brackets correspond with those on maps 1 & 2 (rural areas).

Table 32: Oesophageal cancer mortality in Scotland: urban/rural differences

<u>Males</u>	Population 1971	Observed deaths (1970-1974)	Expected deaths	SMR	Chi ² (trend)*
Cities	811 355	379	336.57	113	
Large Burghs	475 900	185	172.64	107	
Small Burghs	493 570	215	205.41	105	
Districts of Counties	738 735	252	314.89	80	
					15.59 (p<0.001)
<u>Females</u>					
Cities	918 990	348	324.50	107	
Large Burghs	495 540	174	150.63	116	
Small Burghs	542 380	183	191.19	96	
Districts of Counties	758 445	208	246.45	85	
					15.01 (p<0.001)

New Towns were omitted from this table for reasons explained in section 7.3.1

* See Statistical Appendix for method used to calculate trend.

(Section 7.3.0 Part 2: Maps, continues overleaf.)

7.3.1 The New Towns: problems of classification

It is difficult to place the New Towns on an urban/rural scale. Administratively the New Towns are the result of amalgamating five small burghs and their adjacent districts of county. Physically, the New Towns are a mixture of older, denser centres of population (the small burghs) and more dispersed development on 'greenfield' sites. In terms of crude population density the New Towns occupy a middle position between the large burghs and the sparsely populated rural areas, a fact which should make them interesting subjects for comparison. However, two aspects of the New Towns make comparisons difficult: their populations in 1971 were both small and atypically youthful. Apart from East Kilbride NT (pop. 64,115), the New Town populations in 1971 ranged from just over 40,000 in Irvine to less than 15,000 in Livingston. Small populations mean that even one or two deaths more or less than expectation may make a large difference to death rates. In four of the New Towns younger age groups were predominant in 1971; only Irvine had a sizeable established population at the time of its designation as a New Town. Young populations notwithstanding, the New Towns overall had a significantly high male SMR for oesophageal cancer in 1970-74 (SMR 180, $p < 0.001$). Female mortality was slightly elevated (SMR 123) but the result was not statistically significant.

Table 33: Distribution of oesophageal cancer deaths in Scotland by local government area.

The five New Towns.

New Town	Sex	Population 1971	Observed deaths (1970-1974)	Expected deaths	SMR	Chi ²	Significance level
Cumbernauld	M	15 510	7	2.49	281	-	p<0.05 (+)
	F	16 035	6	1.96	307	-	p<0.05 (+)
East Kilbride*	M	31 555	15	6.89	215	9.23	p<0.01 (+)
	F	32 560	7	5.47	128	-	-
Glenrothes	M	13 450	3	2.48	120	-	-
	F	13 885	1	1.88	53	-	-
Irvine	M	20 685	10	6.94	144	-	-
	F	20 760	3	5.48	55	-	-
Livingston	M	6 770	1	.93	108	-	-
	F	6 785	2	.63	318	-	-
<hr/>							
All New Towns	M	87 975	36	19.91	181	13.00	p<0.001 (+)
	F	91 010	19	15.50	123	-	-

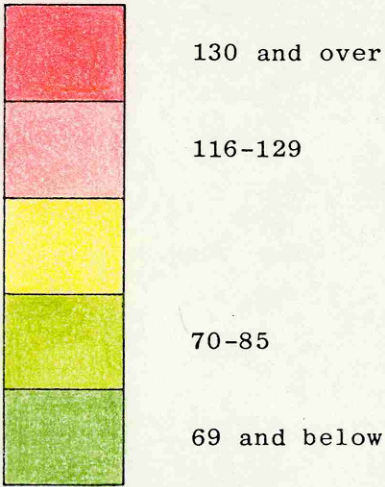
* See note on East Kilbride in section 7.3.2.

7.3.0 Distribution of oesophageal cancer by local government area

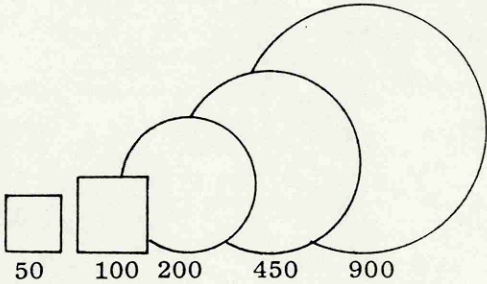
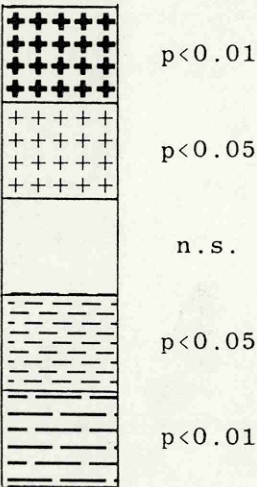
Part 2: MAPS 1 - 6

KEY TO MAPS

Standardised Mortality Ratios



Significance levels

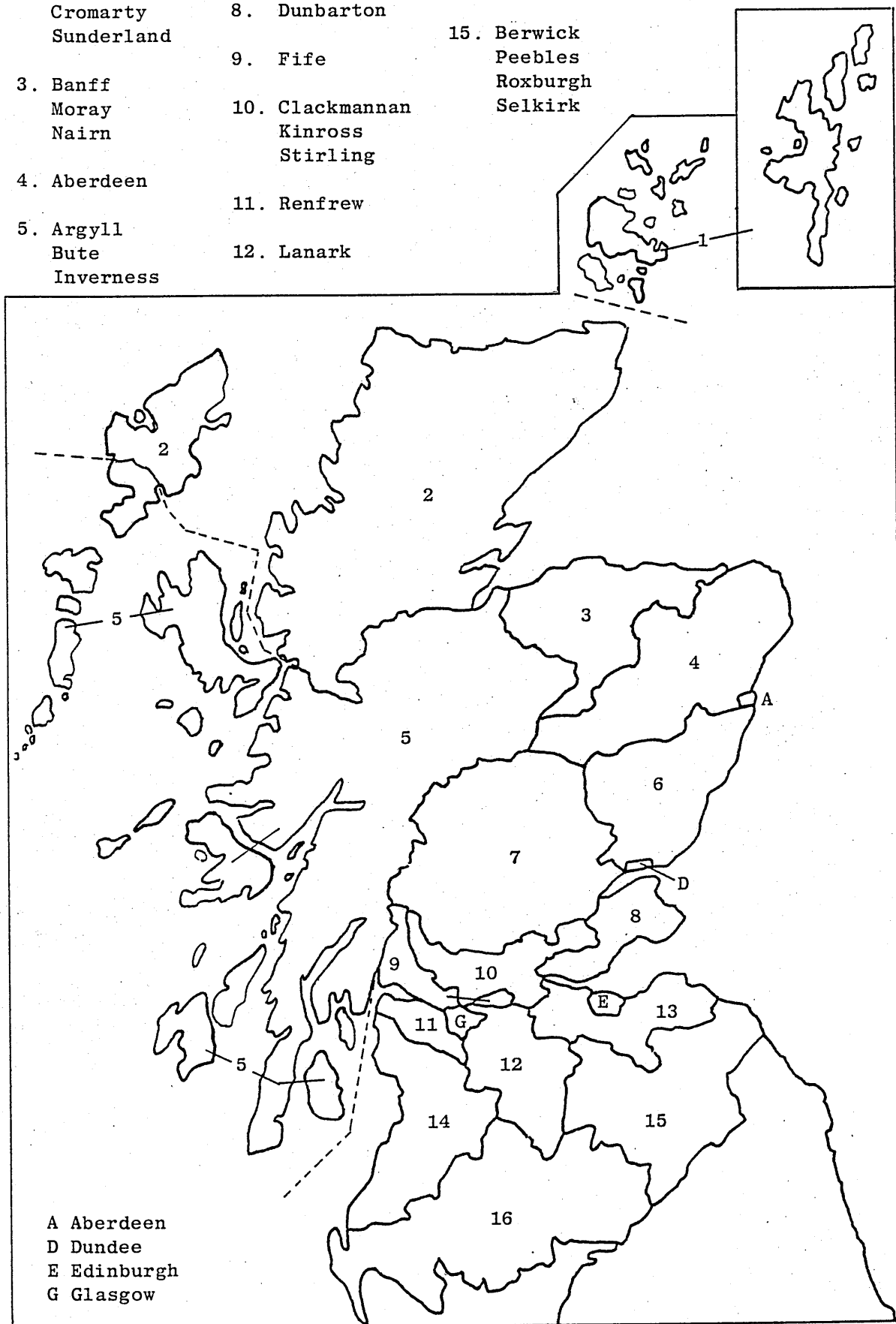


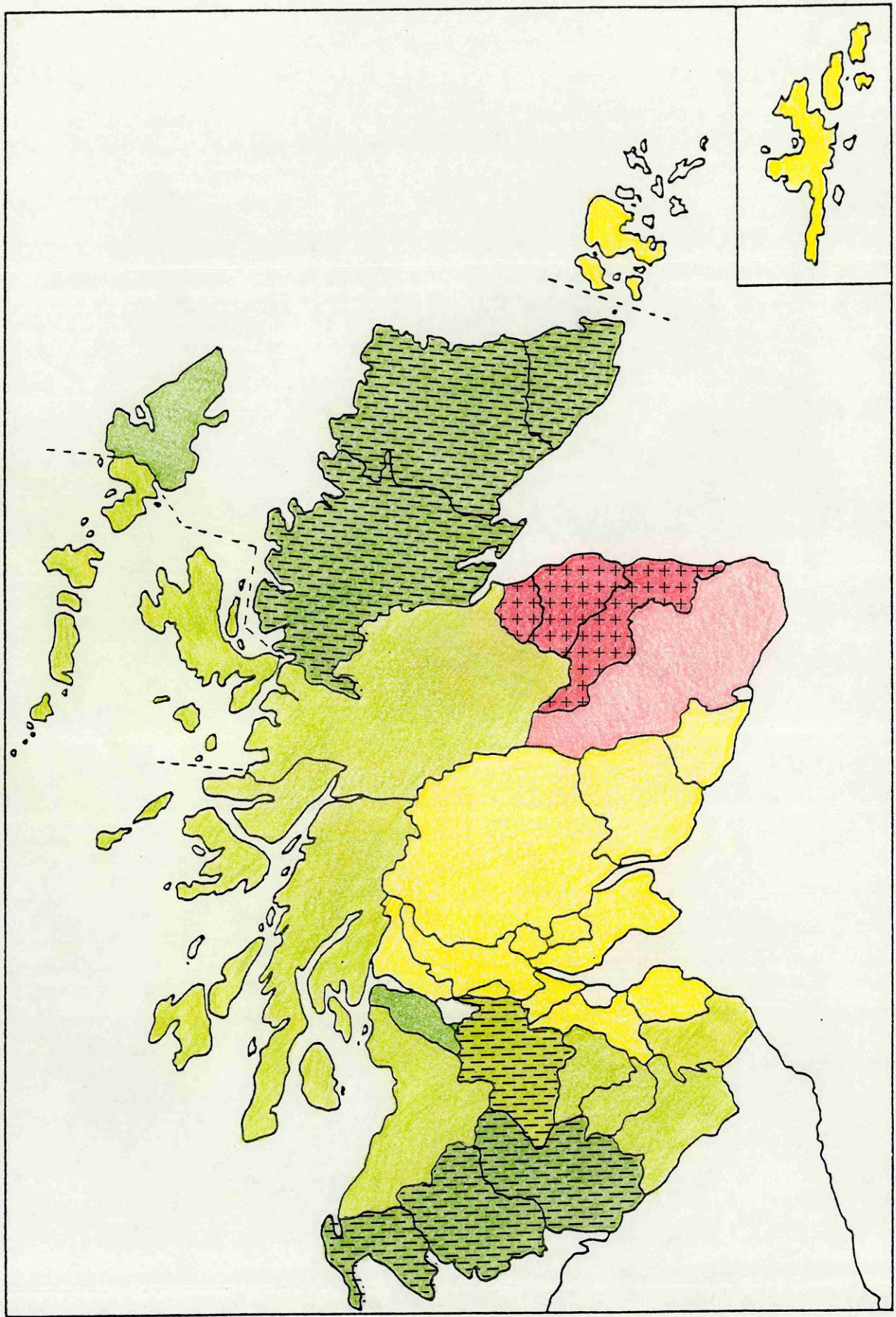
Population size in thousands (maps 1 & 2)

Squares = large burghs, circles = cities.

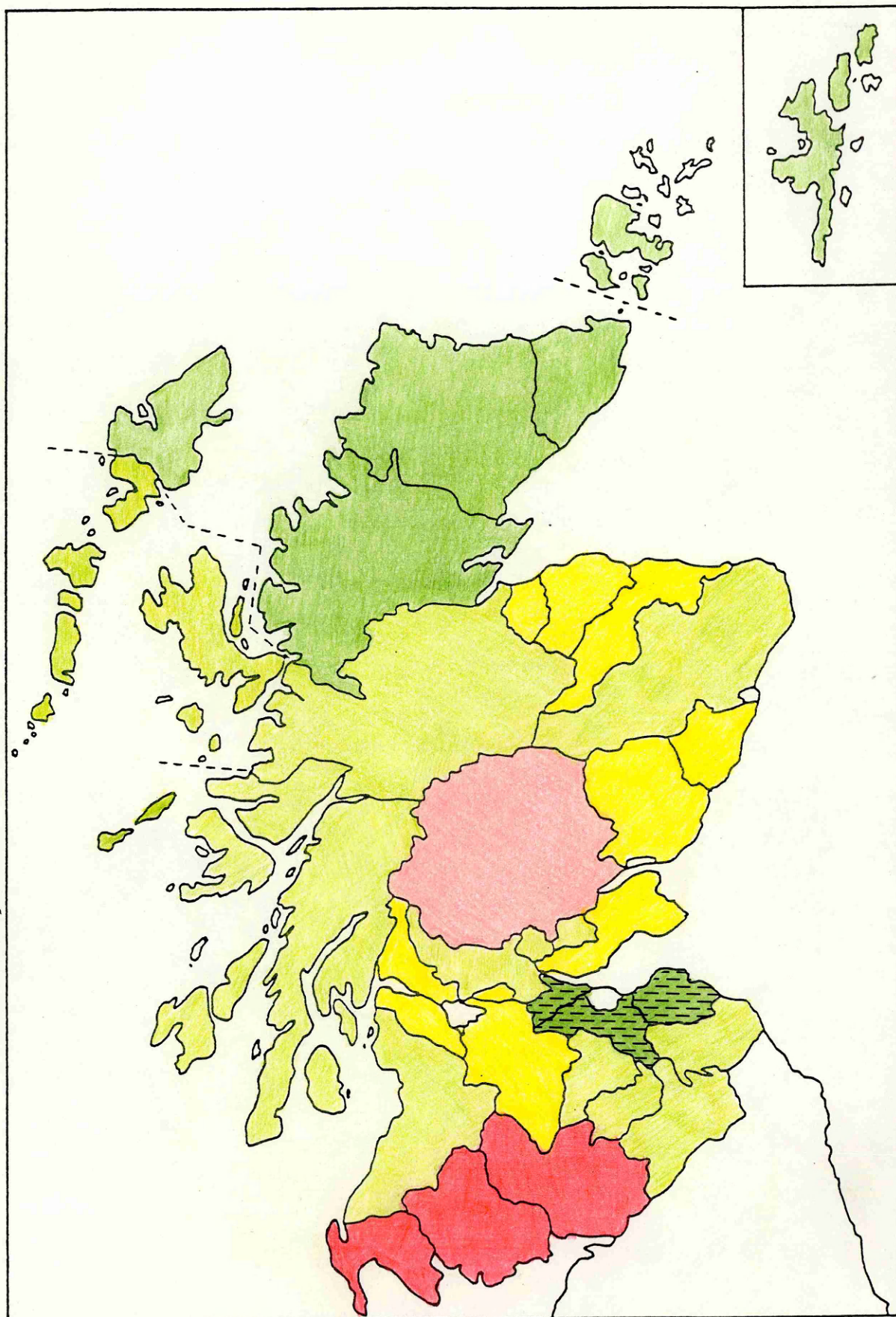
New towns not shown: populations too small for significance tests to give reliable results.

- | | | | |
|--|--|---|--|
| 1. Orkney and
Zetland | 6. Angus
Kincardine | 13. East-
Mid-
West Lothian | 16. Dumfries
Kirkcudbright
Wigtown |
| 2. Caithness
Ross and
Cromarty
Sunderland | 7. Perth | 14. Ayr | |
| 3. Banff
Moray
Nairn | 8. Dunbarton | 15. Berwick
Peebles
Roxburgh
Selkirk | |
| 4. Aberdeen | 9. Fife | | |
| 5. Argyll
Bute
Inverness | 10. Clackmannan
Kinross
Stirling | | |
| | 11. Renfrew | | |
| | 12. Lanark | | |

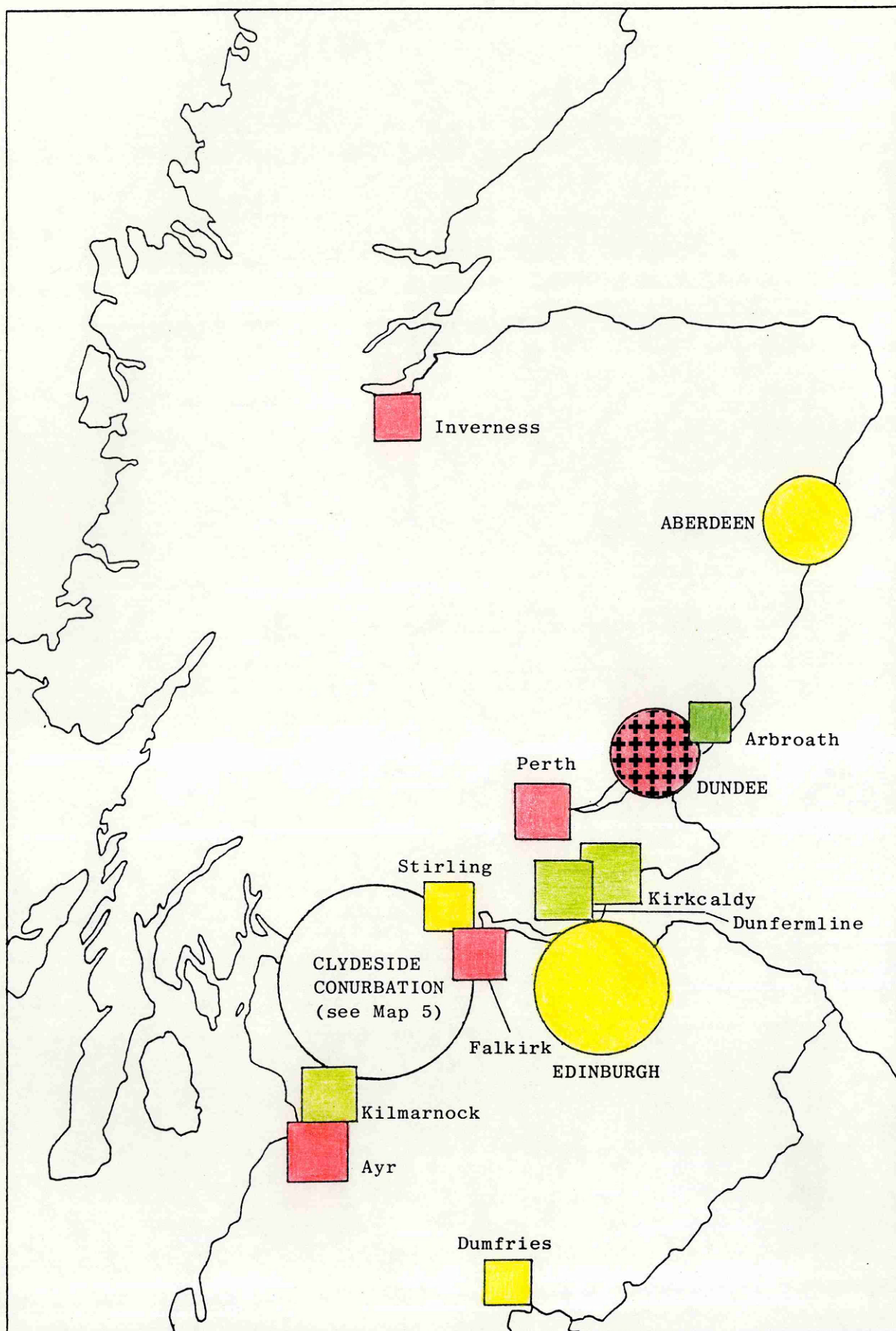




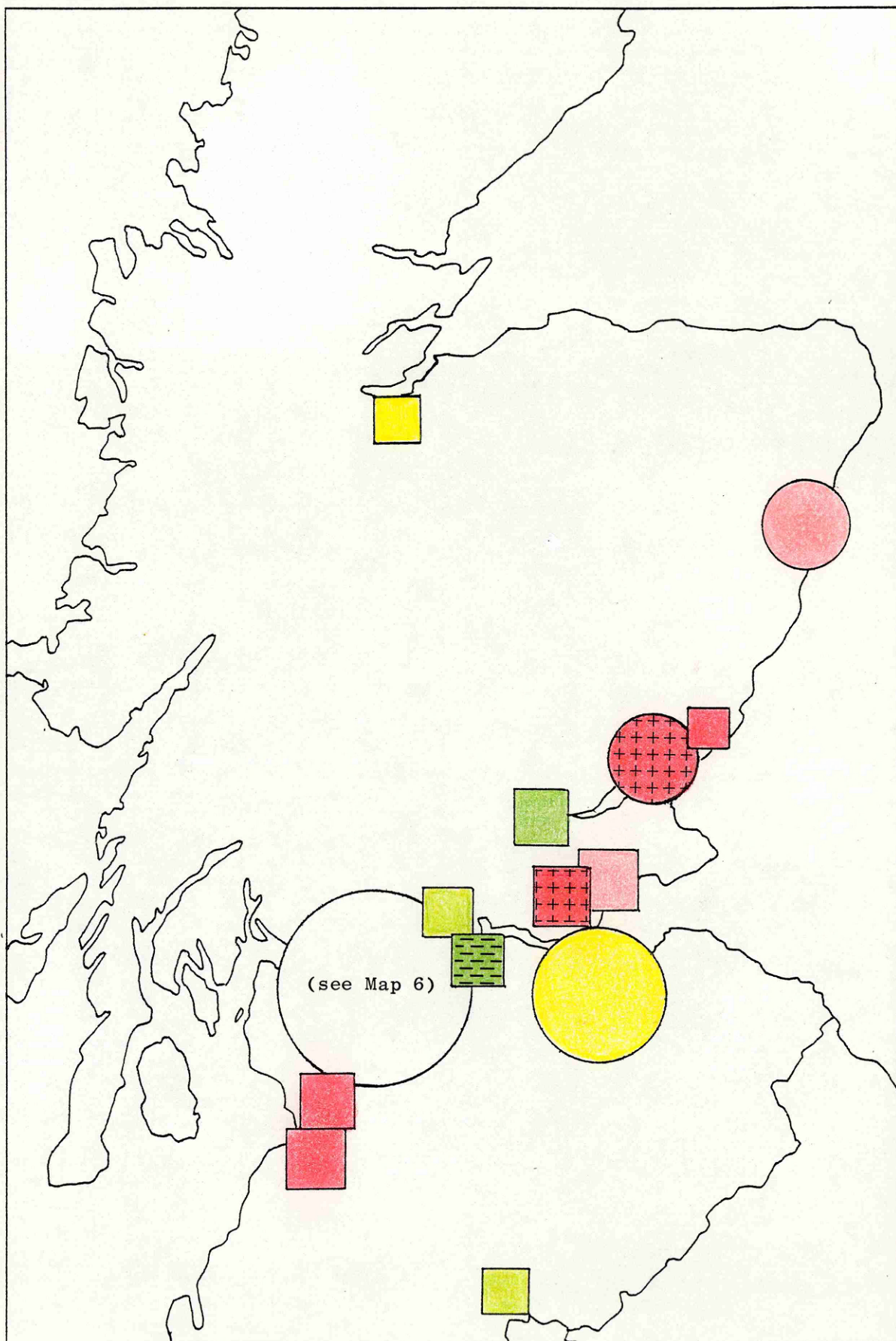
MAP 1: OESOPHAGEAL CANCER, SCOTLAND (1970-1974): MORTALITY IN RURAL AREAS: MALES (See preceding map for key)



MAP 2: OESOPHAGEAL CANCER, SCOTLAND (1970-1974): MORTALITY IN RURAL AREAS: FEMALES



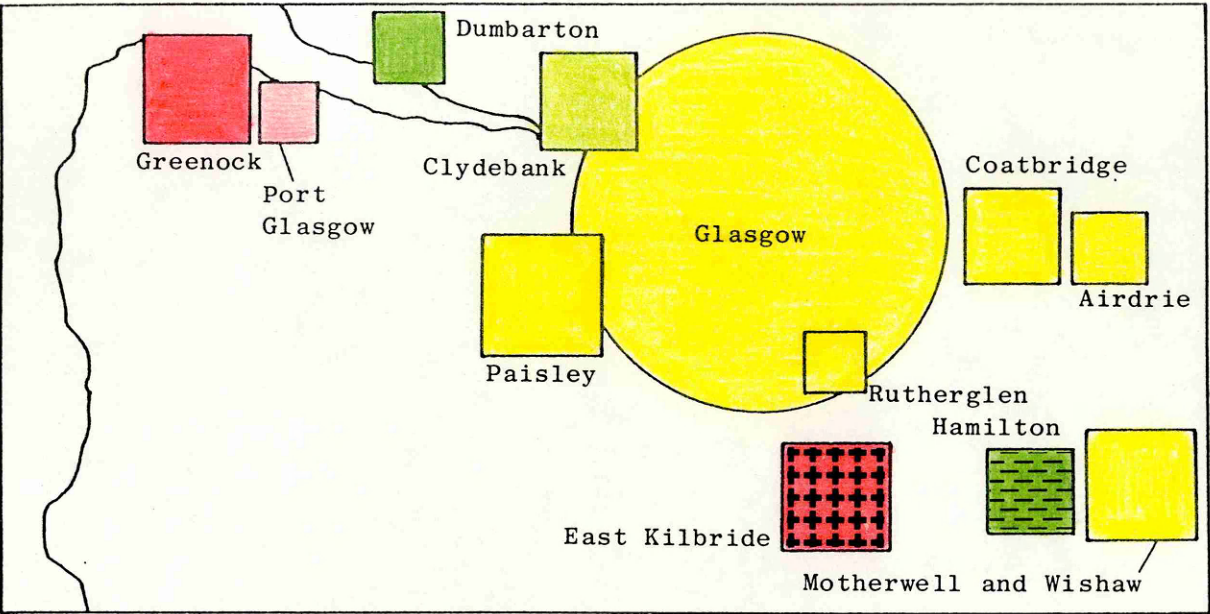
MAP 3: OESOPHAGEAL CANCER, SCOTLAND (1970-1974): MORTALITY IN THE CITIES AND LARGE BURGHs: MALES



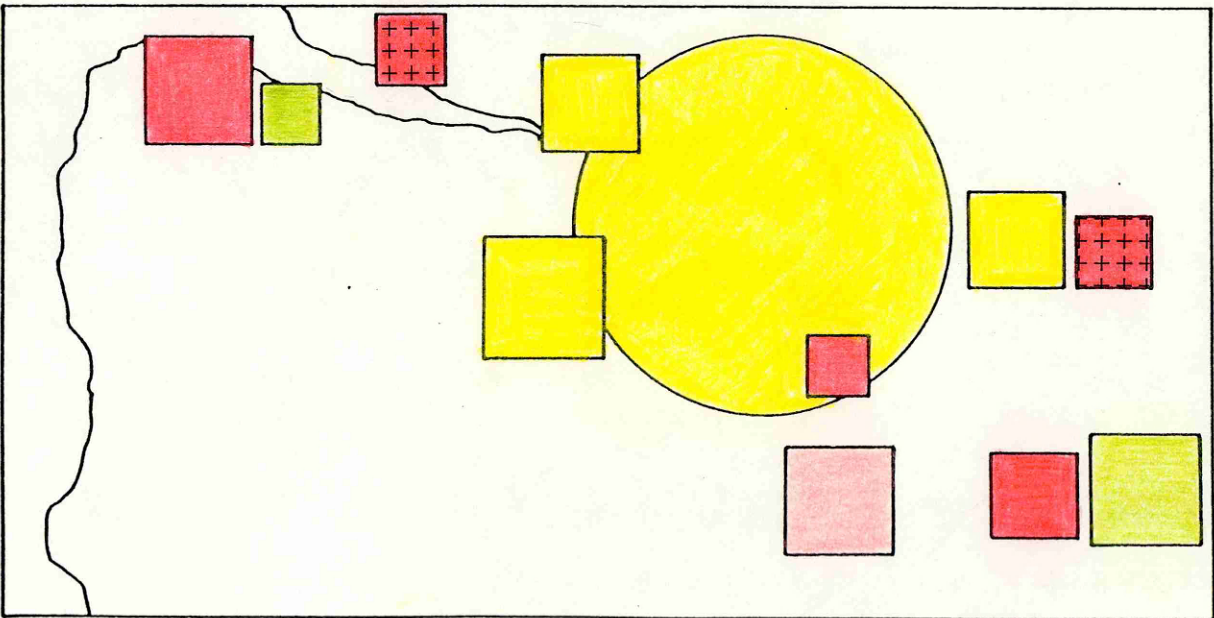
MAP 4: OESOPHAGEAL CANCER, SCOTLAND (1970-1974): MORTALITY IN THE CITIES AND LARGE BURGHs: FEMALES

OESOPHAGEAL CANCER MORTALITY IN THE CLYDESIDE CONURBATION (1970-1974)

MAP 5: MALES



MAP 6: FEMALES



7.3.2 A note on East Kilbride New Town/Large Burgh

For the purposes of this study East Kilbride New Town (NT) and East Kilbride Large Burgh (LB) have been treated as one and the same. The NT was created in 1948 from three Districts of County (DCs): East Kilbride DC, Number 4 DC and Number 8 DC. By 1963 East Kilbride DC had acquired Small Burgh status, and by 1970 Large Burgh status. The large burgh was thus a later and distinct administrative unit within the already existing New Town.

At the 1971 Census, numbers 4 and 8 DCs together contributed less than one per cent of the total NT population. Because of the negligible difference in population size between the NT and LB, and because no deaths from cancers of the mouth, larynx and oesophagus were recorded in the two small DCs in 1970-74, it was decided not to calculate SMRs for the NT and LB separately: the SMR quoted is actually that of the LB.

7.4.0 Interim discussion

When SMRs were calculated for each class of local authority there emerged an almost perfect correlation between degree of urbanisation and oesophageal cancer mortality: the gradient, moreover, was equally strong for both sexes (see Table 32). Similar urban/rural gradients have been observed in the United States and over much of Europe (see section 1.2.1), so that the emergence of this pattern in Scotland was not unexpected. However, when oesophageal cancer mortality is examined by area the neat relationship seen above breaks down and the picture

becomes very confused.

Looking at the maps the most striking feature of the distribution of oesophageal cancer in Scotland is the almost complete absence of spatial concordance between the sexes. With the exception of the rural areas of Caithness, Ross & Cromarty and Sutherland, three or four large burghs and - most notably - the city of Dundee, a high or low SMR for one sex is seldom matched by a correspondingly high or low SMR for the other sex. Some areas, indeed, are remarkable for displaying opposite extremes. Wigtown, Kirkcudbright and Dumfries had the highest female SMR in rural Scotland (SMR 133, n.s.) and the lowest statistically significant male SMR anywhere in Scotland (SMR 53, $p < 0.05$). The large burghs of Arbroath, Dumbarton, Dunfermline, Hamilton, Kirkcaldy and Kilmarnock all had low male and high female SMRs, while Perth, Port Glasgow and Stirling large burghs had high male and low female SMRs. Steep gradients and sharp borderlines are a noted feature of oesophageal cancer incidence throughout the world, but why there should be such a marked lack of concordance between SMRs for the sexes from one area to the next in Scotland is far from clear.

If the underlying causes of the disease are environmental one would expect the sexes to be similarly affected and, though differing perhaps in degree of susceptibility to the risks, for their SMRs to move in parallel. Any major divergences from this pattern would be likely to occur in the smaller populations, where a few deaths more or less than expected may have a large effect on the SMR. With 372 small burghs and

rural districts it was possible that unstable rates in these areas might account for the lack of concordance between male and female SMRs in Scotland. To test this proposition the author looked at the 41 geographical units listed in Tables 29-32 and compared population size with percentage disagreements between male and female SMRs: there was only slight evidence of the anticipated effect of scale ($r = 0.35$). While chance variations in the numbers of deaths in the smaller population units may go some way to explaining the observed pattern, the difference between male and female SMRs was considerable in some large as well as small populations. Scotland is not alone in showing a lack of spatial concordance between the sexes for oesophageal cancer rates: out of hundreds of local authorities in Japan, perhaps only 20 or so have high rates in both sexes (Shigematsu, 19).

7.5.0 Areas with raised oesophageal cancer mortality

The following descriptions refer to the results shown in Tables 29-33 and Maps 1-6.

Of the cities, Aberdeen has a raised SMR for females and Edinburgh a raised SMR for males, but neither is statistically significant. Only Dundee has SMRs which are both high and statistically significant for both sexes.

14 of the 21 large burghs have SMRs over 115 for one or other sex, though none has a statistically significant SMR for both sexes.

Airdrie and Dunfermline have high SMRs for women (194 and 177 respectively), both significant at the $p < 0.05$ level. East Kilbride has a very high male mortality (SMR 215, $p < 0.01$) and a high but not statistically significant ratio for women. Other than East Kilbride, Cumbernauld is the only New Town to have high and statistically significant SMRs (male SMR 281, $p < 0.05$; female SMR 307, $p < 0.05$).

Two groups of rural areas emerged with single-sex SMRs above 130, and two with SMRs above 115, though only one result was statistically significant (Group 3, Nairn, Moray & Banff: male SMR 154, $p < 0.01$). One of the rural groups (Group 16, Wigtown, Kirkcudbright and Dumfries) had a raised SMR for women (SMR 133) which was not far short of statistical significance at the $p < 0.05$ level. Groups 3 and 16 were investigated further (see below) to discover whether deaths were distributed generally or clustered in high-mortality foci.

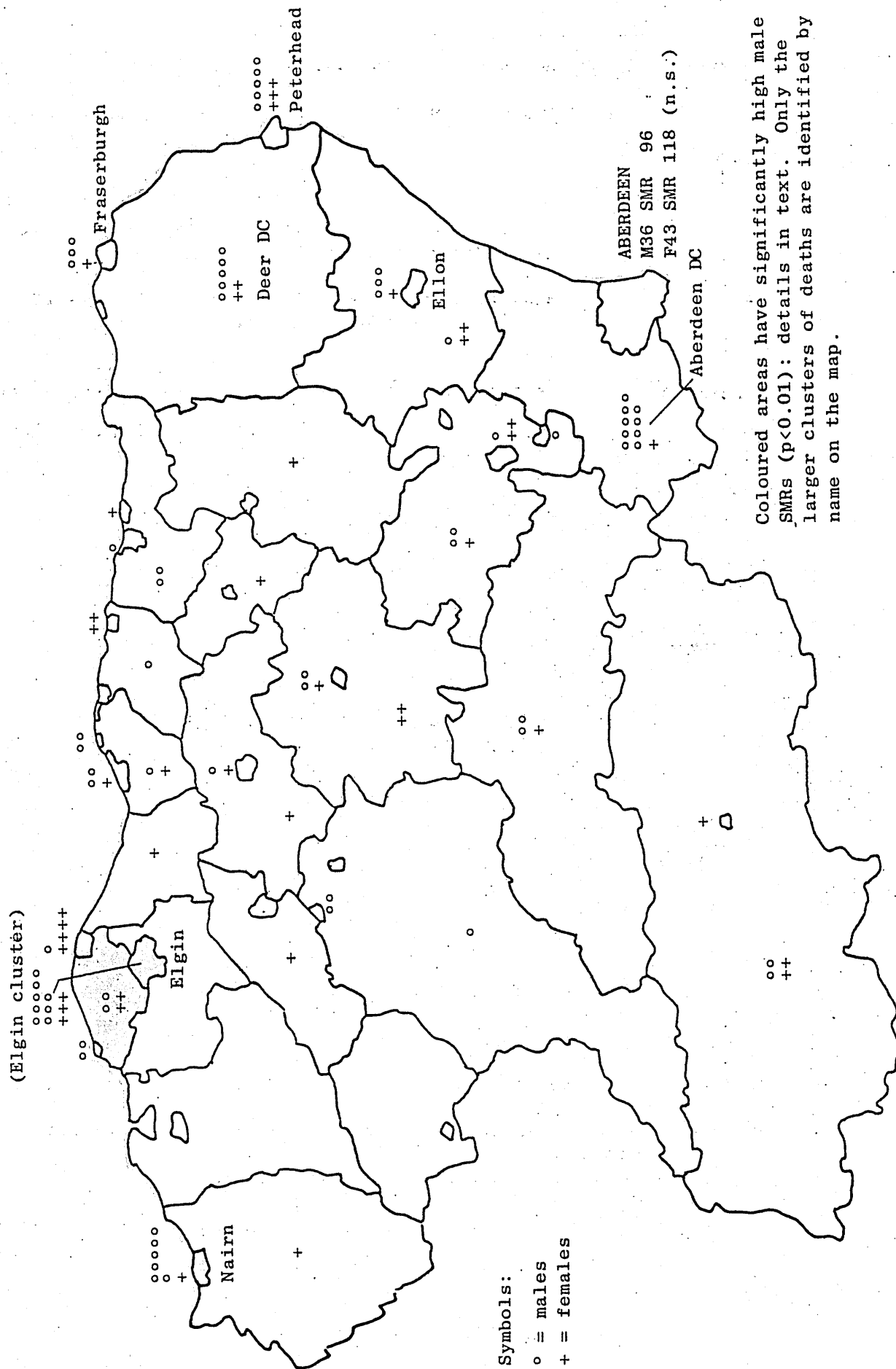
7.5.1 Distribution of deaths in two high-mortality rural areas:

1) Group 3: Nairn, Moray and Banff

The three-county group of Nairn, Moray and Banff shows a considerably raised SMR for males (SMR 154, $p < 0.05$) and an unremarkable result for women (SMR 101). Of the 31 local authority areas which make up this group, 15 have no oesophageal cancer deaths at all for the years 1970-1974: clearly, within the group there must be areas with rates far above normal. When deaths are plotted on a map, two concentrations immediately become visible: Nairn SB and a cluster of small burghs and rural

Overleaf: Map 7 (facing page 243)

MAP 7: DISTRIBUTION OF OESOPHAGEAL CANCER DEATHS (1970-74) IN NAIRN, MORAY, BANFF AND ABERDEEN COUNTIES



districts to the north of, and including, Elgin SB. Between them these two locations account for 19 male deaths (54%) and 9 female deaths (47%).

TABLE 34: Distribution of male oesophageal cancer deaths in Nairn, Moray and Banff.

Area	Population 1971	Observed deaths (1970-1974)	Expected deaths	SMR	Significance level
Nairn SB	5,200	6	1.26	477	$p < 0.01$ (+)
Elgin cluster*	14,858	13	4.95	262	$p < 0.01$ (+)
Remainder of rural areas in group	31,720	16	16.64	97	-

* Elgin cluster comprises Burghead SB, Elgin SB, Lossiemouth & Branderburgh SB, and Duffus & Drainie DC.

Females rates in Nairn and Elgin small burghs are well below the male, in fact below the national average (Nairn SB female SMR 78, n.s., Elgin SB female SMR 94). On the other hand, the high female ratio in Lossiemouth & Branderburgh SB helps bring up the female SMR of the Elgin cluster as a whole (female SMR 187, $p < 0.05$).

Nothing immediately suggests itself as a possible causal factor behind this small north-easterly concentration of deaths. The area encompasses most of the Strath Spey/Glen Livet malt whisky distilling areas, and Elgin SB is prominent as a grain whisky town. On the other hand, Rothes & Knockando, Dufftown and Grantown-on-Spey are also important 'whisky towns', yet none of these has a single oesophageal cancer death for the period in either sex. The alcohol-producing areas are discussed in section 7.7.4.

Nithsdale

The publication of the Atlas of Cancer in Scotland 1975-80 (IARC/Cancer Registries of Scotland, 1985) in the last weeks of this study led the author to reappraise the Nithsdale cluster - dismissed as not worth further study on the page opposite. In the six years covered by the Atlas there were 29 male and 29 female cases in Nithsdale and the annual standardised incidence rates of 10.3 and 5.3 per 100 000 for males and females respectively were among the highest for any area during this period. With such a small population the possibility that random variations unduly influenced the results cannot be excluded. Two points are of interest, however: The first is that a lead/cancer association has emerged (albeit tentatively) a number of times in this study, so it is perhaps significant that lead ore production was a major local industry as late as the early 1950s (Stamp, 1958). It would be reasonable to expect, therefore, that surface deposits and surface water would contain high levels of lead, as in other old lead-producing areas. Second: when the maps in this study are compared with those in the Atlas, it becomes clear that the spatial pattern for the disease is unstable (a point already made in connection with two Welsh studies (section 1.5.3)). For this reason alone the persistence of high rates in one area over two consecutive periods would arouse interest. When that same area is found to have associations with the lead industry it begins to look as though the cluster merits closer inspection.

2) Group 16: Wigtown, Kirkcudbright and Dumfries

In this group the highest rural SMR for females (SMR 133, n.s.) accompanies the lowest male SMR anywhere in Scotland for males (SMR 53, $p < 0.05$). When deaths are matched to areas it becomes evident that a cluster of 19 deaths along the River Nith and the Upper Solway Firth accounts for more than half (59%) of the total female deaths in the group. However, the same towns also contain 67% of the total female population and the female SMR of the town at the centre of the cluster (Dumfries LB) is actually below that of the surrounding area (SMR 74, n.s.). In contrast, Annan and Sanquhar small burghs and Gretna and Upper Nithsdale districts of county have rather high SMRs, and it is these areas which are responsible for elevating the overall female SMR for the three counties. The total number of cases is small, however, and the significance levels low: there was no single area or cluster of areas in this group where the mortality was worth further investigation.¹

The possibility that errors in compiling mortality data might account for some of the variations in areal mortality is discussed - and discounted - in the next section.

7.6.0 Correct attribution of deaths to usual place of residence

Failure to transfer deaths at sea or in institutions to the usual place of residence could have a distorting effect on areal mortality, particularly for uncommon diseases: this matter was touched upon in connection

¹ See note on facing page.

with sea fishing in section 6.3.3. Gardner et al (1984) refer to the instance of Stone Rural District near Stoke on Trent where, for three years, deaths in a newly established terminal care home were included in the rural district returns rather than being transferred to the former place of residence. This error had created an extreme example of bias in the data.

As yet, no similar error has been detected in Scottish data, nor, using Scottish procedures, is it likely that such errors could occur. Deaths in Scottish old people's homes are transferred to the normal place of residence unless the deceased were resident in the home for more than one year. All other institutional deaths are transferred to the usual place of residence unless the deceased were resident in the institution for more than ten years. With an average survival time of six months from diagnosis it is unlikely that many oesophageal cancer patients would be in terminal care long enough for the institution to be regarded as their usual place of residence. The General Register Office was not aware of any large-scale instances of deaths incorrectly assigned, as at Stone RD.² It would appear that incorrectly assigned deaths can be ruled out as an explanation for unexpectedly large clusters of deaths.

7.7.0 Some occupational influences on the spatial distribution of oesophageal cancer in Scotland

In the previous chapter three occupations emerged with significantly high SMRs for men: sea fishing, seafaring and dock work. In sections

2. J. Hannah, General Register Office for Scotland, personal communication, 1985.

7.7.1 and 7.7.2 below, the author has examined the extent to which deaths in these occupations have affected oesophageal cancer mortality in the coastal areas. Many of the coastal fishing towns also have distilleries (or had in the early 1970s³) and, although alcohol manufacture did not emerge as a high-risk occupation for oesophageal cancer, the possibility that a 'downstream' effect exists which might influence areal mortality has also been explored.

Section 7.7.3 looks briefly at two important whisky-producing areas, but discovers no firm evidence of increased oesophageal cancer mortality.

In Table 29 Dundee is shown with significantly high SMRs in both sexes, the substantial number of deaths enhancing confidence in the significance test results. Because of Dundee's historical importance as a centre of jute manufacture the possibility of a connection between jute and oesophageal cancer is considered in section 7.7.4: without, however, producing any strong evidence of a causal relationship.

7.7.1 The fishing industry and its influence on oesophageal cancer mortality in Scottish coastal small burghs

1) Selection of areas for analysis

In the following exercise analysis has been confined to the coastal small burghs: districts of counties were excluded as many of these spread too far inland for deaths recorded in them to be ascribed with confidence to

3. See note on sources of information on Scottish industries overleaf.

SOURCES OF INFORMATION ON THE LOCATION OF SCOTTISH INDUSTRIES.

The most detailed account of industry by locality in Scotland is the Gazeteer of Scotland by W & A.K. Johnston (Johnston & Bacon Limited, Edinburgh), 1958 edition. Where possible the continuing existence of an industry into the 1970s was verified in Bartholomew's Gazetteer of the British Isles, 1977 edition.

Additional information on local industries was taken from two books by Nigel Tranter in The Queen's Scotland series (Hodder & Stoughton): The Heartland: Stirlingshire, Perth & Clackmannashire (1971), and The Eastern Counties: Aberdeenshire, Angus & Kincardineshire (1972).

Tranter's books are prefaced by the statement that the author visited all places mentioned in the texts in the two years preceeding publication: they are thus invaluable for verifying the existence of industries in the counties covered, up to 1969-70.

Information on the jute industry was obtained from the Association of Jute Spinners and Manufacturers, Park Mill, 99 Douglas Street, Dundee. Historical records of the jute industry are held by the University Archivist, University Library, Dundee University.

General information on the fishing industry is available from the Sea Fishes Industry Authority, 10 Young Street, Edinburgh.

Maps locating all malt and grain whisky distilleries operating up to 1969 may be found in David Daiches' Scotch Whisky: its past and present (Fontana), revised edition, 1976.

the coastal region. Cities and large burghs were excluded for a different reason: their populations and patterns of industry are too large and complex for the influence of a relatively small industry like fishing to be discernible. Only in towns where fishing is or was a major industry is there a hope of gauging its effects on mortality.

East and west Scotland have markedly different characteristics, therefore data from east and west coast towns are analysed separately. Apart from Thurso small burgh (1971 population 9,085) the north coast of Scotland is very sparsely populated and is not investigated here.

2) The east coast small burghs

There are 50 small burghs on the Scottish east coast, of which 28 were listed as having fishing concerns up to 1971 (Bartholomew, 1977). In 1971 the east coast small burghs had a total population of 263,930 (128,480 males, 135,450 females), and between them contributed 116 oesophageal cancer deaths (66 male, 50 female) in the years 1970-74. These numbers are just large enough to provide adequate cell numbers when the data are disaggregated into various categories.

Three categories of coastal small burgh are examined:

- towns with both fishing and alcohol industries
- towns with an alcohol industry but no fishing
- towns (predominantly resorts) with neither a fishing nor an alcohol industry

A fourth category - fishing towns with no alcohol industry - proved too small for analysis to be a practical proposition.

If the fishing and alcohol industries do exert an influence on areal mortality, then it would be expected that towns with both industries would show higher oesophageal cancer SMRs than towns without either: it would also be reasonable to expect that towns with one or other industry might have SMRs in between. Analysis of the data suggests that such a gradient may exist, at least among males. The results, however, have a low level of statistical significance and there is neither consistency between the sexes, nor between the east and west coasts. The results from the analysis of east coast data follow below:

TABLE 35: Oesophageal cancer mortality in Scottish east coast small burghs 1970-74

<u>Males</u>	Population 1971	Observed deaths	Expected deaths	SMR*
towns with fishing and alcohol industries	77,590	43	33.81	127
towns with alcohol industries only	56,785	23	24.22	95
towns with neither fishing nor alcohol industries	29,530	17	22.22	80
all east coast SBs (M)	128,480	66	58.03	114
all Scottish SBs (M)	485,540	215	204.41	105
<u>Females</u>				
towns with fishing and alcohol industries	83,130	28	30.80	91
towns with alcohol industries only	52,320	22	22.40	98
towns with neither fishing nor alcohol industries	27,665	18	19.84	91
all east coast SBs (F)	135,450	50	52.18	96
all Scottish SBs (F)	542,380	182	191.19	95

* None of the SMRs was statistically significant at the $p < 0.05$ level.

3) The west coast small burghs

There are fewer towns on the west coast than on the east, but on average their populations are larger (average population of west coast towns 7,100: east coast towns 5,200). Stornaway, Oban, Campbeltown and Stranraer are or were important fishing ports, with some fish also landed at Rothesay, Girvan and Annan (Johnston & Johnston, 1958). There are docks at Ardrossan and ship building/breaking at Troon: Oban, Cove and Kilcraggan, Largs and Stranraer are steamer ports. Of the seven fishing ports listed above, three (Oban, Campbeltown and Girvan) also have distilleries. The tabulated mortality data give the impression that death rates in the west coast small burghs must be rather low: indeed, only Campbeltown and Annan, with 3 and 5 deaths respectively, stand out from the rest (neither town, however, has a significantly high mortality ratio). For this reason SMRs for the west coast small burghs as a whole have been calculated, but no attempt has been made to disaggregate the data for fishing towns, distillery towns or resorts, etc.

TABLE 36: Oesophageal cancer mortality in Scottish west coast small burghs, 1970-74

	Population 1971	Observed deaths (1970-1974)	Expected deaths	SMR*
males	71,215	26	34.85	77
females	78,600	32	34.63	92

* Neither SMR was significant at the $p < 0.05$ level.

7.7.2 Discussion

The picture which emerges from the above analysis is far from uniform. Oesophageal cancer mortality among east coast women and among both sexes on the west coast is below average. Only east coast men show the anticipated mortality gradient: high SMRs in towns with fishing and alcohol industries, low SMRs in towns with neither fishing nor alcohol industries.

In 1971 some 67% of Scottish fishermen lived on the north-east coast and in Orkney and Shetland (Scottish Sea Fisheries Statistical Tables, 1971), the remainder were scattered along the south-east coast, the west coast and Hebrides. Despite a very high oesophageal cancer SMR for Scottish fishermen as a whole, there were probably too few of them living on the west coast for their deaths to have much impact on mortality. Male oesophageal cancer rates are low throughout the west of Scotland rural areas (small burghs included) and in the absence of a large fishing community west coast mortality rates are little different from those inland.

On the east coast, however, deaths among fishermen do appear to have had a discernible effect on mortality. Fishing was the largest occupational category (16.4%) among men who died from oesophageal cancer in the east coast fishing towns: only four other occupations (baker, carpenter, fitter and policeman) had even two deaths each, the remaining deaths were each associated with a different occupation.

If the presence or absence of the alcohol industry in the east coast towns makes any difference to the oesophageal cancer rates, then the effect must be felt downstream from the point of manufacture: of the 116 victims only one worked in the alcohol industry.

7.7.3 Dock workers and seafarers (other than fishermen)

The drift of men with unstable personalities into sea- and shore-based industries had been documented by Plant (1979) and Hore (1982), and foreign studies have emphasised the high alcohol-related disease and accident rates of dock workers (Naeve et al, 1973), merchant seamen (Gulbrandson & Jensen, 1967) and sailors (Schuckit & Gunderson, 1974). This pattern is repeated in Scotland, where dock workers and seamen suffer high mortality from a wide range of diseases and have some of the highest SMRs for oesophageal cancer (see section 6.3.3). However, Scottish dock workers and seamen are relatively few in number (9,660 in 1971⁴) and probably account for less than two per cent of the male population of the major ports. Of the 19 oesophageal cancer deaths in these two occupations, 8 were in Glasgow and 4 in Dundee.

7.7.4 Alcohol production

As late as 1970 most large towns in Scotland had at least one brewery (Bartholomew, 1971), while Daiches (1976) lists 15 grain- and 114 malt-whisky distilleries operating up to 1969. Alcohol production, however,

4. Extrapolated from the 1971 Census, 10% Sample.

is not labour-intensive and -notwithstanding the large number of enterprises - there were little more than three and a half thousand male workers in the industry in 1971.⁵ Despite the apparently strong links between alcohol and oesophageal cancer, alcohol workers seem scarcely more at risk from the disease than the general population.⁶ In the period 1970-74, occupation unit 080 (brewers, wine makers and distillers, etc) furnished only three cases of oesophageal cancer (all male): this number differed little from expectation.

Nor, as far as cancer of the oesophagus is concerned, does there appear to be any evidence for a 'downstream' effect of alcohol production upon local populations. Analysis of mortality data from several distilling towns yields inconclusive results. Two whisky-producing areas in particular were examined: the western distilleries of Skye, Islay and Campbeltown, and the eastern distilleries of Strath Spey and Glen Livet: the results of the analysis are as follows:

Western distilleries: In 1971 the combined population (male and female) of Skye, Islay and Campbeltown was approximately 16,600. During 1970-74 there were only seven oesophageal cancer deaths (5 male) and the SMRs for all three areas combined were below average in both sexes (male SMR 92, female SMR 52, n.s.).

5. J. Salmond, Vital Statistics Branch, General Register Office, Scotland, personal communication 1984.

6. The situation among Scottish alcohol workers appears in striking contrast to that seen among Danish brewery workers (Jensen, 1979 & 1980). Jensen found unequivocal evidence of a positive relationship between length of time worked in a brewery and the risk of developing oesophageal cancer. Male brewery workers had an SMR of 225 compared with males in general ($p < 0.01$) and the relative risk of men working 30 or more years in the brewery was 2.39 ($p < 0.01$).

Eastern distilleries: The Strath Spey and Glen Livet region includes areas with above- and below-average oesophageal cancer mortality. Eleven deaths (8 male) occurred in 1970-74 in the grain-whisky distilling town of Elgin (male population 7,725): the male SMR was 250 ($p < 0.01$). On the other hand, the malt-whisky distilling towns of Dufftown, Grantown-on-Spey and Rothes and Knockando had not a single oesophageal cancer death in either sex in 1970-74.

A separate category for 'distillers and spirit compounders' (unit 239.1) now exists in Scotland, though not in England and Wales. By taking a long time series it might be possible to determine whether or not there are different cancer risks attached to brewing and distilling. However, as category 239.1 was not available in 1971, and as the occupational data for the period covered in this study does not differentiate between the various types of alcohol production, the author has taken the investigation of the alcohol industry no further.

7.7.5 Jute, flax and cotton manufacture

Dundee is the major centre of jute production in the United Kingdom: it is also the only Scottish city to have significantly high oesophageal cancer SMRs in both sexes. This association alone would have prompted a closer look at the other jute processing areas, but there is in addition the known, strong association of workers throughout the fibre and textile industry with alcohol abuse. Donnan & Haskey (1977), for example, found that male textile workers in England and Wales had an SMR of 300 for alcoholic cirrhosis of the liver in the years 1959-63.

Information on jute manufacture and jute-related industries (rope and carpet making) was obtained from the trade association in Dundee.⁷

Because of the textile industry/cirrhosis association, centres of flax and cotton production in Scotland were also included, using Bartholomew (1977) as the guide to industry location.

As late as 1975, ten other Scottish towns - apart from Dundee - had working jute mills or enterprises associated with jute production: all were situated along the north-east coastal strip where above-average mortality from oesophageal cancer was detected. The ten towns were: Arbroath LB, Carnoustie SB, Dunfermline LB, Inverbervie SB, Kirkcaldy LB, Leven SB, Monifieth SB, Montrose SB, Musselburgh SB and Newburgh SB. Three of the above towns also had flax or cotton enterprises (Inverbervie, Monifieth and Montrose) and an eleventh town (Cupar SB) had a flax and linen mill but no jute manufacturing. Oesophageal cancer SMRs were calculated for all eleven towns and for both sexes: the results are tabulated below.

TABLE 37: Oesophageal cancer mortality in eleven Scottish textile towns, 1970-74

	Population 1971	Observed deaths	Expected deaths	SMR
males	86,550	29	38.14	76
females	94,655	42	34.49	122

7. D.A. Borrie, Association of Jute Spinners and Manufacturers, personal communication, 1984.

There were 71 oesophageal cancer deaths in the jute towns during 1970-74 and the combined population of the towns exceeded 180,000. These figures should be large enough to render the effects of chance variations very small, yet once again there is a large and inexplicable disparity between the SMRs for the sexes. The male SMR is low, despite the fact that at least six of the towns also had fishing concerns and/or distilleries. Three of the towns (Carnoustie, Moniefieth and Montrose) are also resorts, with a large excess of elderly women over elderly men (overall, the female population of the eleven towns is some 10% higher than the male). Female mortality from oesophageal cancer was above average (SMR 122), though the numbers were not quite large enough to give the SMR statistical significance. Unfortunately, gaps in the occupational information for the 42 women who died from oesophageal cancer make it difficult to determine how many - if any - had been employed in the textile industry. It may well be that deaths in these occupations contributed to the raised female SMR for these towns, but the data do not allow this to be confirmed.

7.8.0 Other cancers

The maps of Howe (1970 & 1979) show that there is little or no homogeneity in the distribution of cancers in the United Kingdom, a picture confirmed by the more recent maps of cancer mortality in England and Wales of Gardner et al (1984). Areas with high mortality from one type of cancer may have below-average rates for other cancers, even those which might be assumed to be related in some way (e.g. cancers at sites

along the alimentary tract). The vagaries of cancer distribution prompt Howe (1979) to remind us that cancer is not one disease '...but a general name for many malignant neoplasms, each with its own pathology and aetiology.' All the same, it is curious that even cancers of the alimentary tract should show such a lack of concordance, and not only in the United Kingdom: Mesle (1984) remarks that, in Europe, '...the map representing mortality by cancer of the stomach is an almost perfect negative of the one for mortality of the intestine.'

In Scotland, not one of the areas with significantly high mortality from oesophageal cancer (listed in Tables 29-31) also had significantly high mortality from cancers of the mouth or larynx. A few areas had above-average SMRs for mouth cancer in males (e.g. Armadale: 476, Cumbernauld: 174, Elgin: 272) but the numbers were small and none of the SMRs achieved statistical significance. Dundee, location of the highest statistically significant SMRs for oesophageal cancer, had below-average SMRs in both sexes for laryngeal cancer and for female mouth cancer, and only a slightly raised SMR for male mouth cancer (SMR 115, n.s.). With reference to the prefatory note to Chapter Six: the results of comparing oesophageal cancer mortality with mortality from cancers of the mouth and larynx show that any association between the three cancers - at least in Scotland - is weak or non-existent.

Three of the areas with high mortality from oesophageal cancer (Dundee, Nairn and Wigtown) are, however, shown in Howe (1979) with above-average or high mortality from a range of other cancers. Dundee has a significantly high mortality for cancers of the intestine and rectum in males,

Table 38: Relationship of oesophageal cancer SMRs to proportions of manual workers and car owners in 25 Scottish urban areas.

Area	Cars/100 households	Manual workers/ 1000 households	Male SMR	Female SMR
Aberdeen*	44.3	616.4	96	118
Airdrie	42.3	708.6	86	194
Arbroath	44.5	677.9	68	154
Ayr	54.3	534.1	149	144
Clydebank	30.9	758.8	83	185
Coatbridge*	34.7	730.3	85	92
Dumbarton	40.3	693.4	66	210
Dumfries	52.2	602.7	112	74
Dundee*	39.2	675.8	155	141
Dunfermline*	49.3	599.6	74	177
East Kilbride*	61.4	531.4	215	125
Edinburgh*	44.0	517.8	114	99
Falkirk	44.7	681.2	134	45
Glasgow*	25.8	683.7	107	103
Greenock*	34.0	725.9	138	143
Hamilton	44.6	628.5	52	147
Inverness	56.1	538.1	129	107
Kilmarnock	49.3	657.5	80	131
Kirkcaldy	47.8	677.8	74	129
Motherwell & Wishaw*	40.7	694.9	87	63
Paisley*	37.1	693.7	88	91
Perth	48.1	538.3	141	68
Port Glasgow	29.3	828.1	120	77
Rutherglen	38.3	619.8	112	161
Stirling	48.8	599.7	107	77

* Ten largest towns by population size.

Correlations:	All urban areas	Ten largest areas
Manual workers and male SMRs:	$r = 0.20$	$r = 0.30$
" " " female "	$r = -0.23$	$r = -0.32$
Car ownership and male SMRs	$r = 0.32$	$r = 0.49$
" " " female "	$r = -0.05$	$r = -0.25$

Sources: Data on car ownership and proportions of manual workers collated from 1971 Census material and kindly supplied by the Regional Heart Survey (Derek Cook, Department of Clinical Epidemiology and General Practice, Royal Free Hospital, London. Personal Communication). Oesophageal cancer SMRs: the author.

as well as for stomach cancer in both sexes. Nairn, with a high male SMR for oesophageal cancer, also has high ratios for male stomach cancer and female breast cancer. Wigtown, with an above-average SMR for cancer of the oesophagus in females, also has a high ratio for breast cancer and for cancers of the stomach, intestine and rectum in males.

7.9.0 Are spatial patterns of social class and wealth reflected in spatial patterns for oesophageal cancer?

The strong overall correlation between social class and oesophageal cancer (described in section 6.3.5) is not reflected in the geographical pattern. The author looked at the proportions of manual workers (expressed as numbers of manual workers per 1000 households) in the cities and large burghs (25 areas in all) and compared them with the corresponding SMRs. Given the lower incomes of manual workers compared with non-manual workers and the known poorer health experience of people in lower income groups, the author expected to find a strong positive correlation between the proportion of manual workers and SMRs: the results did not bear out this expectation. For males the correlation was weakly positive ($r = 0.20$): for females weakly negative ($r = -0.23$). (See Table 38 opposite for the data on which the calculations in this section are based.)

Things were scarcely clearer when SMRs were compared with car ownership.⁸ Again, since manual workers in general earn less than non-manual workers,

8. Car ownership is often used as a measure of relative prosperity between areas. However, because of urban/rural differences in the provision of public transport - and consequent variation in the need for private transport - the measure is probably best reserved for comparing like with like: e.g. all urban or all rural areas.

common sense suggests there will be a negative correlation between the proportion of manual workers and car ownership. This is certainly true in Scotland, where the correlation in the cities and large burghs is strongly negative ($r = -0.78$). However, when this proxy measure of wealth was tested against area SMRs for oesophageal cancer, the correlation for males was found to be only weakly positive ($r = 0.32$), while for females there was virtually no correlation ($r = 0.05$).

The possibility that chance variations might have affected the results from some of the smaller urban areas led the author to repeat the test using the ten areas with the largest populations: there was little change, other than that the correlation between car ownership and oesophageal cancer emerged slightly stronger for males ($r = 0.49$).

The relationship between oesophageal cancer and wealth appears to differ somewhat from that between cardiovascular disease (CVD) and wealth.

There are strong correlations between CVD and several indices of low income, low status and hardship (e.g. proportion of manual workers, proportion of unskilled workers, large families and unemployment): there is also a strong negative correlation with car ownership (Pocock et al, 1982). Since oesophageal cancer is also known to be associated with poverty and poor diet it might be thought that the gradient of increasing risk for this disease would closely match the gradient of increasing poverty. Up to a point this is what happens in Scotland, but at the bottom of the socio-economic scale the relationship does not hold. In Chapter Six (section 6.3.5) it was shown that males in social class V

had a lower mortality from oesophageal cancer than males in classes III(M) and IV. In this section it emerges that there is a modest correlation between the disease and wealth, at least as inferred from car ownership. An hypothesis to explain the disease/wealth association is advanced in the next chapter (section 8.3.1), only to be demolished by the facts on income and the price of alcohol.

Note: The spatial correlation between oesophageal cancer and liver cirrhosis was examined in Chapter Three (section 3.5.6).

CHAPTER EIGHT: SUMMARY AND CONCLUSIONS

Part One: Summary of main risk factors

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Part Two: Oesophageal cancer in Scotland

- 8.5.0 Social class, occupation and industry
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CHAPTER EIGHT: SUMMARY AND CONCLUSIONS

Part One: Summary of main risk factors

Key points from the literature survey are summarised and related, where appropriate, to the situation in Scotland. References given earlier in the work are mostly omitted here, however, section numbers are given as an aid to cross-referencing. Limited mention is made of papers published or encountered during the writing of this chapter.

8.1.0 Nutrient deficiencies

Wherever oesophageal cancer is endemic, dietary studies have identified low levels of vitamins and trace elements: the deficiencies, however, are not necessarily the same in all areas, nor are nutrient deficiencies confined to high-risk areas (in China, for example, adjacent high- and low-risk groups have been found to share similar nutrient deficiencies). Low levels of most of the important vitamins have been reported in connection with the disease, although it now seems clear that a whole complex of vitamins must be deficient before the risk of the disease is significantly elevated. Similar patterns of trace-element deficiencies have been reported, but three (iron, zinc and selenium) have received more attention than the others.

8.1.1 Iron

The role of iron in oesophageal cancer remains unclear. Several authors have questioned whether the low iron levels in patients are part of the causal process or a consequence of the disease. Van Rensburgh (1985) believes that the evidence on Plummer-Vinson syndrome in Sweden now points to deficiencies of riboflavin,¹ thiamin, pyridoxine, ascorbic acid and selenium, rather than to iron-deficiency anaemia. Results from Iran, however, suggest that iron status is still of crucial importance, particularly during early growth and development (Siassi, 1985). There appears to be no evidence from Scotland to link iron-deficiency anaemia with either Plummer-Vinson syndrome or oesophageal cancer. The absence of Plummer-Vinson cases in areas where widespread anaemia among women was previously noted (section 2.3.6) suggests that progression from iron deficiency to Plummer-Vinson syndrome to oesophageal cancer is not important in the Scottish context, if anywhere.

8.1.2 Zinc and selenium

Several studies (section 2.3.1-2) have identified low zinc levels in oesophageal cancer patients and animal experiments lend strong support to the hypothesis that zinc and/or selenium deficiency enhances susceptibility to carcinogens. Ames (op.cit.: section 5.1.5) provides an explanation of how deficiencies of zinc and selenium may promote carcinogenesis by inhibiting enzyme defence systems. In Scotland, zinc deficiency is most likely to result from enhanced excretion in heavy drinkers.

1. Recent work in China (Thurnham et al, 1985) seems to confirm the importance of riboflavin deficiency.

8.1.3 Lead and cadmium: zinc and selenium antagonists

In section 5.1.4 it was noted that many old lead mining areas have a higher than average mortality from oesophageal cancer: in parts of North Wales the association is particularly striking. In Scotland the defunct lead mining area of Nithsdale has shown above-average oesophageal cancer mortality over two consecutive sampling periods (in itself a noteworthy occurrence - see footnote to section 7.5.1). A problem, however, is that other former lead-producing areas (e.g. Derbyshire and Cumbria) do not have especially high rates for the disease and this fact would seem to exclude a direct causal connection. However, there is growing evidence that lead and its principal contaminant - cadmium - antagonise body zinc and selenium, with the effects described. In imitating some of the effects of poor diet or alcohol-induced nutrient deficiencies, lead appears to behave as a predisposing agent in cancer development. The precipitating factors for oesophageal cancer are remarkably varied but a reasonable assumption is that - while lead predisposes - tobacco provides the precipitating carcinogens. Variations in mortality between lead-rich areas could plausibly be ascribed to local variations in drinking and smoking.

In the period covered by the present study the most likely source of lead in the Scottish population (other than for those working with lead, or living in Nithsdale) would have been tap water in older houses with lead piping. However, the extent of urban renewals since the war and the rapid change from lead to plastic piping in recent years makes it

almost impossible to establish a firm connection between lead in tap water and oesophageal cancer.

8.1.4 Nutrient deficiencies: Summary

In a recent paper, van Rensburg (op.cit.) correctly states: 'No consistent patterns of gradients have emerged whereby nutrient deficiencies could account for geographic differences in oesophageal cancer.' This, however, is far from saying that nutrient deficiencies do not affect the development of the disease: on the contrary. The consensus of views (summarised in Day, 1984 and van Rensburg, op.cit.) is that while the precipitating factors may vary from place to place, and the exact nature of the nutrient deficiency may also vary, impaired nutritional status is an essential predisposing factor in all oesophageal cancer.

National Food Surveys and Family Expenditure Surveys show that people in social classes III(M)-V tend to eat less well than those in social classes I-III(N). However, the levels of nutrient deficiencies routinely reported from regions where oesophageal cancer is endemic are lower by far than anything seen in the United Kingdom. It is unlikely that many people in Scotland have food intakes low enough to give rise to deficiency symptoms: any problems arising from low intakes are likely to be found among the elderly rather than the poor.

There are no published data on regional variations in the Scottish diet and extensive enquiries failed to find any research projects on this subject. It is not possible, therefore, to correlate spatial

variations in oesophageal cancer mortality with food consumption, at least for the present.

8.2.0 Carcinogens: polycyclic hydrocarbons, nitrosamines and mycotoxins

National Food Survey data for the United Kingdom show that consumption of salted and smoked foods is slightly higher in Scotland than in England and Wales: however, this is unlikely to have any effect on oesophageal cancer in Scotland. Evidence from Iceland and Baltic countries, where consumption of smoked foods is far higher than in Scotland, suggests that polycyclic hydrocarbons have a strong effect on the stomach but scarcely affect the oesophagus at all.

Although there have been striking results from animal experiments, clinical and epidemiological research in many countries has failed to prove a causal connection between nitrosamines and oesophageal cancer in humans. A more encouraging line of enquiry appears to be the fungal contamination of food.

Mycotoxins from Alternaria, Fusarium and Aspergillus species are of proven mutagenicity and carcinogenicity and one or more species have been found in stored cereals, legumes, pickles and condiments in three endemic regions (Transkei, Iran and northern China) and in Japan (section 2.1.7). The author has found no suggestion that fungal contamination of food plays any significant part in cancer promotion in Britain.

8.2.1 Other ingested carcinogens

In endemic areas there are strong associations between oesophageal cancer and exposure to snuff, betel quids, bracken and the siliceous bran of certain cereals. In the West some occupations (e.g. asbestos and metal workers, dyers and rubber vulcanisers) carry a very high risk of the disease, but for the general population the most important oesophageal carcinogens are probably those contained in tobacco tars.

8.3.0 Alcohol

While there is no firm evidence to implicate alcohol itself as a carcinogen, there is a growing body of evidence to suggest that chronic heavy drinking predisposes the body to carcinogenic attack by inducing nutrient deficiencies. Among very heavy drinkers nutrient deficiencies can affect even individuals whose diet would normally be considered adequate. The less well-fed (who may include people on low incomes or the elderly) can incur nutrient deficiencies at lower levels of alcohol consumption.

In Scotland there is a clear link between oesophageal cancer and social class, with the risk for manual workers more than three times that of non-manual workers. Lack of regional or cross-sectional data makes it difficult to determine whether alcohol and/or tobacco alone are responsible for the increased risk, or whether other factors such as low incomes and poor diet also play a part. Regional variations in a number of diseases may, in part, reflect variations in alcohol consumption which,

in turn, may be a product of regional differences in the 'drinking culture'. The work of Breeze (1984) sheds light on drinking cultures and has relevance for the present study.

Breeze (op.cit.) found that two attributes in particular distinguish high-risk² from low-risk areas:

high-risk areas have a larger proportion of manual workers (this accords with findings in the present study) and a larger proportion of drinkers spending a greater proportion of time in bars (beer drinking in bars accounted for more than 90% of alcohol consumption in high-risk areas).

That alcohol problems flourish among bars and drinking clubs is hardly surprising: what is interesting is that so much of the drinking in high-risk areas is a communal activity. Despite the drinking environment, however, Breeze found no evidence of 'heavy-drinking subcultures' which condone aberrant or antisocial drinking. While a drinking culture may favour generally high levels of consumption, the emergence of deviant drinkers is almost certainly governed by factors peculiar to the individual, not the culture (see below, section 8.7.0).

8.3.1 Heavy drinking and income

In section 7.9.0 it was noted that the positive association between oesophageal cancer and low income did not appear to hold at the very bottom of the socio-economic scale. The author speculated that income

2. The risks concern liver cirrhosis, mental illness and drunkenness offences, not oesophageal cancer.

differentials between the social classes might have been such that, while heavy drinkers in classes III(M=-V had sufficient money to finance their habit, would-be heavy drinkers in class V could not afford to drink heavily and so avoided a major risk factor for oesophageal cancer. Contemporary data on alcohol prices and income, however, lend no support to this hypothesis.

In 1971 the average price of a pint of beer in the United Kingdom was 11.5p (Brewers Society Statistical Handbook, 1984) and gross weekly earnings (all full-time manual workers aged 21 and over) were £30.93 (Social Trends, January 1973). The threshold of risk for oesophageal cancer appears to fall somewhere above 50 units of alcohol per week³ or the equivalent of 25 pints of beer (see section 3.4.0 for definitions of alcohol units, and section 3.5.7 for a discussion of the risk thresholds). To have been in the oesophageal cancer risk group, the 1971 drinker would have needed to spend £2.88 or more per week. This baseline figure represents less than one tenth of the weekly income of the average manual worker and, although disaggregated figures are not available, it seems probable that even the lowest paid groups in social class V could have afforded to drink heavily had they so wished. Inability to afford alcohol is unlikely to be behind the lower oesophageal cancer mortality seen in social class V.

3. This is not a fixed threshold: it may be lower in the case of heavy smokers or higher for non-smokers.

8.4.0 Tobacco

Although not absolutely proven, the overwhelming probability is that tobacco provides the carcinogens which precipitate oesophageal cancer among susceptible individuals in Western cultures. The emphasis is important because in cultures where alcohol consumption is limited or proscribed tobacco has not emerged as a strong risk factor (section 4.1.0).

The present consensus is that tobacco and alcohol act synergistically to increase the risk of oesophageal cancer far beyond that posed by either substance on its own (sections 4.1.0 and 4.1.3). The majority of drinkers are also smokers (section 4.3.1), so a reasonable assumption is that heavy drinkers not only predispose themselves to cancer but also supply the carcinogens which precipitate the disease. There has been some research into regional variations in tobacco consumption in Scotland (section 4.3.1) but the data are insufficient to permit tests of correlation with oesophageal cancer.

* It is theoretically possible that some - perhaps all - of the statistically 'significant' results in this study may be the product of chance alone. In any 20 tests at the $p < 0.05$ level the probability of finding at least one statistically significant result is considerable, even where the data contain no 'real' discrepancies and the null hypothesis is in fact true. The risk of getting spurious results is lessened (but not eliminated) by selecting higher levels of statistical significance, though this in turn raises the possibility that genuine effects may be excluded because they do not reach the extreme levels of significance. Problems relating to the 'significance of significance tests' are summarised and discussed in Jones and Rushton (1982).

Part Two: Oesophageal cancer in Scotland

The main points from the Study Section are summarised and discussed. The author's findings are compared with those of Kemp et al (1985) and the many dissimilarities noted. No statistically significant* spatial correlates of oesophageal cancer were found for the years 1970-1974 and it is argued that this is because the distribution of the disease in Scotland was, and still is, completely random. It is further argued that this randomness reflects the mode of occurrence of a susceptible 'type' in the population.

8.5.0 Social class, occupation and industry

Oesophageal cancer in Scotland correlates very strongly with social class and with degree of urbanisation: however, there is little trace of these relationships in the spatial distribution of the disease. Similarly, although some occupations and industries have a significantly high mortality from the disease, most have no effect on the spatial pattern.

In most British empirical research occupation defines social class, so that a strong correlation between cancer and social class would seem to imply a similar correlation between cancer and occupation. In practice the connection exists but only in the most general form: non-manual occupations (which define social classes I-III(N) have much lower SMRs for oesophageal cancer than manual occupations (social classes III(M)-V). When individual occupations are examined, those with high mortality

* See note on opposite page.

appear to have little in common, save that all come within the category of manual work and some have associations with heavy drinking. Since no specific risk factors emerge from the occupations themselves and since manual work itself cannot be considered a cancer risk, the increased risk attached to men in social classes III(M)-V must be associated with the men themselves, their lifestyles or their environment.

With the exception of sea fishing, no industry or occupation in Scotland has any influence on the spatial pattern of oesophageal cancer (sections 7.7.1-5). Alcohol, although a major risk factor, appears to have no effect on the disease at the point of manufacture: none of the principal distilling areas had a significantly high mortality in either sex in the period investigated by the author (however, Kemp et al (1985) did find higher mortality in the Grampian and Highland distilling regions in the period 1975-1980: see section 8.7.1 below).

8.6.0 Urban/rural differences

As Table 32 (Chapter Seven) shows, there is a pronounced gradient of mortality between town and country in both sexes. To some extent this relationship is carried through into the spatial pattern: the highest statistically significant SMRs in both sexes are found in a city (Dundee) and the lowest SMRs are found in rural areas. There is of course a link between the gradients of social class and degree of urbanisation, in that the most affected groups (social classes III(M)-V) are more numerous in the cities and older industrial burghs than in the suburbs, new towns

and rural areas. When the pattern is examined in greater detail, however, the relationship between mortality, social class and type of area appears far from constant.

8.7.0 Spatial variations

The spatial distribution of oesophageal cancer in Scotland presents a confusing picture. Analysis of the 1970-74 data reveals a pattern in which the majority of areas had extremes of mortality for the sexes: areas where mortality was high or low in both sexes were few, and only one area - Dundee - had SMRs which were significantly high in both sexes. No attempt was made to test the spatial pattern for randomness or non-randomness, as was done by Kemp et al (reviewed below).⁴ On visual inspection, however, the maps show no sign of clustering in either sex, in which respect they resemble those in Kemp et al (op.cit.).

8.7.1 Temporal instability in the spatial pattern

The Atlas of Cancer in Scotland 1975-1980 (Kemp et al, 1985): hereafter called 'the Atlas') was published when the present work was very near completion. A comparison of the oesophageal cancer maps in the Atlas with those in this study reveals few similarities. Far from introducing unwelcome contradictions, however, the timely publication of the Atlas has provided support for the author's view that there are no

4. Join-count statistics, whether they use free or non-free sampling techniques, require an expected value for the number of joined pairs in a hypothetical random pattern. Calculating the expected value is a lengthy iterative process: to produce a value for Scotland - with its 399 pre-1975 local government areas - would have required computational facilities not available to the author. An introduction to join-count statistics may be found in Ebdon (1977).

current geographical correlates of oesophageal cancer in Scotland because the disease in that country is not primarily influenced by environmental factors (with the possible exception of lead in the Nithsdale area).

Among rural areas Kemp et al found high male rates⁵ in Inverness, Angus, Nithsdale, Clackmannan and the Shetland Isles. Of these areas, only Nithsdale had a high (though not statistically significant) SMR in the present work. In the Atlas, female rates were high in the eastern borders, south Ayrshire, Clydesdale and south Lothian: in this study none of these areas shows a high mortality for females.

In the Atlas the Grampian and Highland distilling areas have high rates for oesophageal cancer (albeit based upon very few cases). In the present study none of the four main distilling areas had a high mortality from the disease, indeed the western distilling area had below-average SMRs in both sexes (section 7.7.4). However, if three alcohol- and tobacco-related cancers are compared (mouth, larynx and oesophagus), the Atlas maps give a definite impression of an arc of moderate-to-high incidence stretching from Skye through Inverness and round the Grampian perimeter to Angus. The arc encompasses the fishing towns discussed in section 7.7.1 and many of the most important distilling areas.

Although the present author found no evidence of an oesophageal cancer

5. Strictly, the maps of Kemp et al are not wholly comparable with those in the present work. The Atlas uses a six-year time series, records incidence rates not SMRs and uses the post-1975 local government boundaries. However, many of the rural boundaries did not change and the cities and many of the large burghs also remain essentially the same. While cross-identifying small areas of high or low incidence/mortality might pose problems, the broad comparisons employed here are not jeopardised by the boundary changes.

risk associated with distilling, the cumulative impression from the Atlas suggests that the industry should be looked at using a much longer time series.

In the Atlas none of the Scottish cities had particularly high rates: certainly Dundee had ceased to be a focus of high mortality. Of the large burghs, only East Kilbride stands out in both studies. In the author's work East Kilbride had a high SMR for females and a significantly high SMR ($p < 0.01$) for males. In the Atlas East Kilbride continues to show high rates in both sexes: the persistence of high rates throughout both study periods makes East Kilbride a town of some interest (without, as yet, anything to suggest why this should be so).

There are three aspects to all the maps discussed here which suggest that the causes of oesophageal cancer in Scotland are not to be sought among external, geographically definable factors:

- marked instability of the spatial pattern in the comparatively short period (11 years) covered by the two studies,
- lack of spatial concordance⁶ between the sexes (strongest in the author's maps but also evident in the Atlas, and
- a complete lack of clustering on both sets of maps.

Like the author, Kemp et al made every effort to minimise the effects of chance (in their case by using a slightly longer time series, rather

6. 'Lack of spatial concordance' refers not to the overall higher male rates (found throughout the world) but to the fact that so few Scottish areas have rates which are simultaneously high or low for both sexes.

than by amalgamating areas with small populations): the random distribution of oesophageal cancer in their maps is therefore unlikely to be due to small numbers.

Kemp et al calculate an 'index of non-randomness' (D) for each map. In this test a score of 20 or more indicates an almost completely random distribution: a score of 10 indicates a very high degree of clustering. An example of a cancer which, in normal circumstances, exhibits a high degree of randomness in its distribution is leukaemia: in the Atlas maps the D scores for leukaemia accord with expectation at 20.05 and 19.03 for males and females respectively. If the author's hypothesis about the essentially random occurrence of alcohol-related cancers is correct, then the D scores for cancers of the mouth, larynx and oesophagus should all approach 20: in the Atlas maps they do (see Table 39 below).

TABLE 39: Tests of non-randomness: 'D' scores for three alcohol-related cancers in Scotland (data for 1975-1980).

	males	females
oral cavity and pharynx	20.03	19.56
larynx	18.83	19.93
oesophagus	17.53	17.63

Source: Kemp et al (1985)

For an explanation of the terms and results see the preceding text.

Possible reasons for the random distribution of these cancers are explored in the next section.

8.7.2 An hypothesis for the random distribution of oesophageal cancer in Scotland

As manual workers make up the majority of oesophageal cancer victims their distribution is obviously an important element in the spatial pattern of the disease. However, if the proportion of manual workers were the only factor involved we should expect to find the spatial pattern remaining stable over longer periods: instead of which the reverse is true. Marked instability characterises the spatial pattern in Scotland, just as it did in the results from earlier Welsh studies (section 1.5.3).

A number of factors - manual occupations, middle to low incomes, restricted diets, drinking and smoking - all appear as background 'constants' to the disease in Western cultures. Where Scotland is concerned, the question should be asked: do these background factors remain constant in their spatial distribution, or might the shifting mortality pattern be explained by migrations among susceptible groups?

It is true that there have been movements away from the declining industrial areas to the newer industries based on North Sea oil and electronics, but these movements cannot explain the unstable mortality pattern. Census data show that migrations have mostly occurred among younger workers in age groups 20-34: older workers tend to have fewer opportunities for career changes and hence less cause to migrate. There are also small post-retirement migration peaks: however, studies have shown that the elderly tend to move only short distances, usually for

reasons of illness or infirmity and to be with or near relations (Fox & Goldblatt, 1982). In short, population movement is unlikely to have had much effect on areal mortality from oesophageal cancer: the larger migrations have involved groups unaffected by the disease, while the elderly have mostly moved within their own areas.

Given that the main risk factors are common, widely distributed and affect many thousands who do not fall prey to the disease: given also that population movements do not seem to influence oesophageal cancer mortality in Scotland, then the existence of areas with mortality significantly different from the norm requires some other explanation. The relative unimportance of clustering on any of the maps, past or present, from England, Wales or Scotland; the absence of spatial concordance between the sexes; the temporal instability of the mortality pattern; the lack of any firm evidence with which to incriminate a specific occupation or any substances other than alcohol and tobacco: all argue for an explanation in which individual behaviour and susceptibility are the crucial factors determining who develops the disease and who remains untouched. What sort of traits might be involved?

Genetic factors can be ruled out in all but a few cases (section 1.2.2) and no evidence has yet emerged to link oesophageal cancer with any particular somatotype. It is not impossible that susceptibility to the disease derives from some innate metabolic defect, though if this were so one would expect a genetic component to be present and perhaps for some evidence of this to show as a clustering effect on maps: no such

effect is seen. If a metabolic defect is present it is more likely to have been acquired in the course of long-term chronic drinking. Clearly, there is an environment which fosters the emergence of a 'susceptible type', otherwise the disease would hardly show such a predilection for a particular band in the social-class spectrum. However, although aspects of the 'physical' environment (poor housing, unemployment, the relative price of alcohol, etc) may exert an influence, chronic heavy drinking is at root a response to purely individual experiences (childhood background, for example, appears to play a crucial role in the development of many heavy drinkers (McCord & McCord, 1960)). No statistical technique can control for the almost infinite number of routes by which individuals become habituated to alcohol and, for all practical purposes, the emergence of heavy drinkers must be regarded as a random process. Though quantifiable in terms of risk, the sequelae of heavy drinking are also largely random in their distribution. There is a psychopathological element in heavy smoking and much of what has been said about the occurrence and consequences of heavy drinking is also applicable to smoking.

8.3.7. Support for the hypothesis

No geographical correlates of oesophageal cancer emerge from the 1970-1974 Scottish data: the author believes that there are in fact none to find and that the distribution of the disease reflects the random mode of occurrence of a susceptible type in the population. The facts as presented already give strong support for the hypothesis: however,

there are at least two ways in which the arguments could be tested. The infallible method - reviewing the case histories of oesophageal cancer victims - is unfortunately not open to the author. An acceptable alternative would be to identify groups of the supposed 'victim type' to ascertain whether their members indeed have a higher mortality from the disease. In fact, five groups containing many who meet the specification have already been examined in this study.

Three sea-based occupations (stevedores, fishermen, and deck and engine room ratings) are known to attract a disproportionate number of men with personality and drinking problems: male bakers and pastry-cooks and female domestics also have high indices for most alcohol-related problems (section 6.3.3). All five occupations in Scotland have significantly high SMRs for oesophageal cancer: for three the significance levels are particularly high (stevedores $p \leq .005$, fishermen, $p < 0.005$, female domestics, $p < 0.001$). These results provide strong support for the author's view that oesophageal cancer in Scotland reflects the distribution of a particular personality type and is little, if at all, influenced by external agents.

8.8.0 Epilogue

If a disease is inherently random in its occurrence, is there any point in drawing maps of its distribution? The answer is probably yes, although only hindsight will show whether a particular exercise was worth the effort. At the start of this study literature on oesophageal

cancer in the United Kingdom was scarce and limited to accounts of the disease in small areas of Wales and (one paper) Edinburgh. It was not known, nor could it have been foreseen, that the wider distribution of the disease would be almost completely random. However, the fact that the present distribution of the disease is random (and apparently the result of unquantifiable behavioural factors) does not mean that this will always or exclusively be so. It is not impossible that some new substance, process or habit will carry an oesophageal cancer risk. Maps are arguably the simplest way to get early warnings of change and even unpromising subjects such as oesophageal cancer should not be neglected. Indeed, given modern technology, routine grid-reference computer mapping of any disease could probably be made cost-effective: monitoring is always preferable to post-mortems.

APPENDIX: STATISTICAL METHOD

The sources and composition of the data used in this study were described in Chapter Six (sections 6.2.0 and 6.3.2): deficiencies in the data and the author's response to them were discussed in sections 6.3.1-3. This appendix deals with such aspects as the criteria governing the choice of areal units and the length of the data series, and with the preparation of the raw data for analysis.

Selection of areal units and time series: general considerations

Note: Frequent reference is made below to the atlases of Gardner et al (1984) and Kemp et al (1985): for the sake of brevity these two works are simply called 'Gardner' and 'Kemp'.

For the major causes of death the rates are likely to be reliable even in small local government areas and for periods as short as one year. The same is not true for uncommon diseases such as oesophageal cancer, where it may be necessary to choose large populations or long time periods in order to minimise the effects of random fluctuations on the rates. Such choices usually involve adjustment and compromise: select too large a population area and important spatial detail may be lost: select too long a time period and time trends may be obscured. There seems little agreement on the correct theoretical approach to making such decisions and, in many works, the final choice appears arbitrary. Neither Gardner nor Kemp justify their choice of time period on other than empirical grounds: Kemp, indeed, hints that the process is one of

educated guessing: e.g. 'The intention was to choose the smallest administrative unit that could be expected to provide reliable rates over a period short enough for time trends to be unimportant.'

Gardner, mapping cancer in England and Wales, selected the pre-1974 local government areas and an eleven-year time series: Kemp chose the post-1975 Scottish administrative areas and a six-year series. In the opinion of the present author, neither time period is suitable for analysing spatial mortality from oesophageal cancer in Scotland. The eleven-year period chosen by Gardner would have obscured the changes in the spatial distribution of the disease which occurred in Scotland during the 1970s, while the six-year period chosen by Kemp - perfectly adequate for the common cancers - is insufficient to provide reliable rates for some of the rarer cancers. For a number of reasons the author adopted a different approach, taking a fixed time period (the 1970-1974 quinquennium) and choosing instead to adjust some of the areal units. In practice this meant amalgamating some of the rural areas so as to achieve, wherever possible, populations of 50 000 persons in each sex. Efforts were made to group together rural areas with similar characteristics, as described in Chapter Seven.

It would have been desirable to have a theoretical basis for selecting 50 000 as the lower population limit for rural areas: the fact is, however, that the choice was arbitrary. The author considered using a method devised by Pompe-Kirn et al (1981) which, it is claimed, makes it possible to measure the size of population below which tests of significance on low mortality levels can have no statistical significance. When applied to the present author's data, Pompe-Kirn's method produces

values very near those already selected by the author (e.g. 46 000 is the minimum value for valid statistical significance at the 5% level). For reasons which need not be detailed here, however, Pompe-Kirn's procedure emerged as suspect and the author decided not to use it to support what had originally been a matter of subjective judgement.

Originally, the author intended to map cancers of the upper alimentary tract over two five-year periods to find out a) if the spatial pattern remained stable over time and b) if there were areas of persistently high mortality which should receive further investigation. Purists might argue that the author should not have chosen consecutive quinquennia, nor have selected a time period starting with 1970, but should have taken quinquennia pivoting on a Census year (e.g. 1971 and 1981). For a variety of reasons this was not possible: The 1981 Census results were not available at the time this study began. Had the first five years' data pivoted on the 1971 Census, the following five years could not have been standardised against reliable population estimates, nor - since the 1981 data were unavailable - could the author have used the average of the two censuses, as was done by Gardner (in passing, neither Gardner nor Kemp use time periods which pivot on a Census year). In the event, the author could not afford to buy the 1975-79 data and had to settle for analysing just one quinquennium.

Use of standardised mortality ratios rather than death rates

Age and sex-specific death rates are essential for anyone wishing to make international comparisons and, for this reason, were used by Gardner and Kemp in their respective atlases. The present author, however, wished only to map the distribution of oesophageal cancer

within Scotland and to measure the statistical significance of any variations which might emerge. For this objective the standardised mortality ratio (SMR) is not only adequate, it is preferable, in that it provides an overall summary statistic which allows the reader to see at a glance which areas have mortality above or below the norm for the population being studied. This approach was also used by Pocock et al (1982) in their analysis of geographic variations in cardiovascular mortality.

Calculation of SMRs

All SMRs, whether for areas or occupations, were calculated by the indirect method: for the criteria governing the choice of direct or indirect method, see McMahon and Pugh (1968).

Areal SMRs were calculated on a CDC 6600 mainframe computer at the University of London Computer Centre, using programmes written by J.Thiedman (revised in 1979 by S.Firsht) for the Epidemiology Monitoring Unit (EMU) of the London School of Hygiene and Tropical Medicine. Warm thanks are due to Sarah Firsht for tuition in the use of the programmes. EMU programmes used are listed at the end of this appendix and identified by bracketed numbers in the text.

Census populations were checked by comparing the summed age-group totals for each local government area with the published area totals for each sex (1): where discrepancies occurred, these were identified and eliminated (2). Scottish (national) death rates for cancers of the mouth, larynx and oesophagus were then calculated by sex and five-year

age group (3). SMRs by sex and local government area were calculated using a further EMU programme (4).

Occupational SMRs: In 1983 the author moved to Sussex and his data was transferred to the VAX computer at Brighton Polytechnic. The author is grateful for permission to use the Polytechnic computer and, in particular, to Ms Elizabeth Colley for assistance in the retrieval of occupational data. In the event, because of pressure on computing facilities, the occupational SMRs were calculated 'by hand' on a Casio fx4000p programmable calculator.

Measuring the urban/rural mortality gradient

The method used to test the statistical significance of the urban/rural mortality gradient in Chapter Seven (Table 32) is a variant of the Mantell-Haenzel procedure devised by Breslaw and Day (1980). Specifically, what is being tested is the trend (expressed as a value of Chi-squared) in the ratio of observed to expected deaths for each class of local government area. The equation is as follows:

$$X_1^2 = (\sum AY - N_1 \sum pY)^2 / N_1 [\sum pY^2 - (\sum pY)^2]$$

Where

	Level				
	Y_0	Y_1	Y_2	
Observed	A_0	A_1	A_2	N_1
Expected	B_0	B_1	B_2	N_2
					T

and $p_i = e_i / \sum e_i =$ expected number in the i^{th} group divided by the sum of the expected numbers.

Maps

In areas with small populations even one or two deaths more or less than expected can produce exaggerated swings in the SMRs, so that mapping by ratio alone can give a very misleading impression. For this reason, the maps in this study also display significance levels, as shown in the Key to the maps. Significance levels throughout the study were calculated according to the criteria laid down by Bailar and Ederer (1964): e.g. where the expected deaths were greater than five the Chi-square test was used (significance levels are for Chi^2 with one degree of freedom): where the expected deaths were five or less the Poisson test was used.

Colours used for the maps are intentionally similar to those used in the Cancer Atlas of Scotland (Kemp et al, op cit): there are, however, fewer shades as the author employs only five class intervals instead of the seven in Kemp's work. As stated, the present author was less concerned to present the even gradations of areal mortality than to map any statistically significant extremes which might shed light on the aetiology of the disease: for this reason SMRs within the range 76-115 have been grouped into one broad class.

EMU Programmes (Programmes produced by the Epidemiology Monitoring Unit
of the London School of Hygiene and Tropical Medicine)

All programmes, except (2), are written by J.Thiedeman (undated),
updated by S.Firsht, March 1979.

(1) STRAGE (Regional): a programme for summing age groups by area and
comparing results with given/published totals.

(2) ALTAPE: Written by Len Greenwood, March 1975. A programme for
altering card image files by changing or deleting characters in a record,
or by adding or deleting whole records in the file.

(3) TRENDS 2: A programme for producing age-standardised rates by the
indirect method.

(4) STAND (Regional): A programme for producing SMRs by area, using
the standard populations and rates computed in (3) above.

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